Functional assessment of haemophilic arthropathy with Three-Dimensional Gait Analysis

Sébastien Lobet

Thesis submitted in fulfilment of the requirements for the degree of "Docteur en sciences de la motricité"

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UNIVERSITE CATHOLIQUE DE LOUVAIN

Faculté des sciences de la motricité

Institute of NeuroScience IoNS

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Sébastien LOBET

Sébastien Lobet was born in June 1976 in Ottignies, Belgium. Sébastien completed his Masters degree in physiotherapy and rehabilitation in 1998 and in sports physiotherapy in 1999 at the Université Catholique de Louvain, Louvain-la-Neuve, Belgium. Being passionate about sports, he wanted, like many young physiotherapists, to treat sportspeople. In 2001, however, while he was working in the orthopaedic surgery department of the Cliniques Universitaires Saint-Luc in Brussels, he met Patrick, his first patient with haemophilia: a meeting which would completely change his career path. Patrick shared his experience as a patient with Sébastien, his everyday difficulties with having constantly painful joints. In the same period of time, Professor Hermans, the head of the brand new centre for the treatment of haemophilia at the Cliniques Universitaires Saint-Luc, suggested Sébastien get involved in the assessment of joint damage in haemophilia patients. This interest soon turned into a calling! This was the start of an inseparable partnership between a physiotherapist and a haematologist.

Between 2003 and 2005, Sébastien specialized in the treatment and musculoskeletal assessment of patients with haemophilia. He took up a 3-month fellowship in the Haemophilia Centre & Haemostasis Unit of the Royal Free Hospital, London and a 2-month fellowship at the Royal Women's Hospital and Royal Children Hospital of Brisbane, Australia. He completed a degree in Pediatric Orthopedic physiotherapy in 2009 at the Université Libre de Bruxelles, Belgium.

Presently, his main research interests lie in the area of musculoskeletal assessment in children and adults with haemophilia. In 2009, he received the Henri Horoszowski Memorial Award at the 11th International Musculoskeletal Congress of the World Federation of Haemophilia, Cartagena de Indias, Colombia for the free paper entitled "Impact of haemophilic ankle arthropathy on gait disability: analysis of energetic and mechanical variables". In 2010, he received the "Heroes in Haemophilia" International Baxter Award for the best poster presentation "An innovative approach of functional assessment of haemophilic arthropathy by three-dimensional gait analysis" at the Moving Forward in Haemophilia Partnerships in Practice Baxter meeting, La Hulpe, Belgium.

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Thank you to all those who encouraged me in these past four years, be it by phone, e-mail, a helping hand or by cooking me a meal. I especially thank my tennis team and my faithful childhood and university friends for whom I was less present, not to mention more quickly tired at the end of the evening! Thank you, my friends, for supporting me so greatly.

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Contents

Index of abbreviations

3D	three-dimensional
3DGA	three-dimensional gait analysis
AH	Arnold–Hilgartner radiological scale
AROM	active range of motion
BMI	body mass index
C_{net}	mass-specific net cost of transport
CoM	centre of mass of the body
E_{ext}	total external mechanical energy of the CoM
E_{kf}	instantaneous forward kinetic energy of the CoM
E_{kl}	instantaneous lateral kinetic energy of the CoM
E_{kv}	instantaneous vertical kinetic energy of the CoM
EMG	electromyography
E_p	gravitational potential energy change of the CoM
FFI-R	Foot Function Index-Revised short form score
g	gravitational acceleration, 9.81 m s^{-2}
GDI	Gait Deviation Index
GRF	ground reaction forces
HA	haemophilic arthropathy
HAT	head–arm–trunk segment
HJHS	Hemophilia Joint Health Score
ICC	intra-class correlation coefficient
ICF	International Classification of Functioning, Disability, and Health
M	body mass
MDC	minimal detectable change
MDC_{95}	MDC at 95% confidence interval
$MDC_{\%}$	coefficient of variation of the minimal detectable change
MJI	multiple joint impairments
MRI	magnetic resonance imaging
MSK	musculoskeletal
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OI	orthopedic insoles

OS	orthopedic shoes
PCA	principal component analysis
PWH	patient with haemophilia
r	factor loading of the principal component analysis
RA	rheumatoid arthritis
RER	respiratory exchange ratio
ROM	range of motion
SD	standard deviation
SEM	standard error of measurement
SEM_{95}	SEM at 95% confidence interval
$SEM_{\%}$	coefficient of variation of the standard error of measurement
S_v	vertical displacement of the centre of mass
TAA	total ankle arthroplasty
THR	total hip replacement
TKR	total knee replacement
US	ultrasonography
V_f	velocity of the CoM in the forward direction
V_l	velocity of the CoM in the lateral direction
V_{O2}	rate of oxygen consumption
V_v	velocity of the CoM in the vertical direction
W_{ext}	external work performed to raise and accelerate the CoM relative to the surroundings
W_{ekf}	positive work necessary to accelerate the CoM in the forward direction
W_{ekl}	positive work necessary to accelerate the CoM in the lateral direction
W_{ep}	positive work necessary to lift the CoM during a stride
W_{ekv}	positive work necessary to accelerate the CoM in the vertical direction
W_{int}	internal work
$W_{int,dc}$	work done by the lower limbs moving against each other during the double stance phase
W_{tot}	total mechanical work
WFH	World Federation of Haemophilia
WHO	World Health Organization
Z	Z-score

Introduction

Haemophilia as a rare hemorrhagic disorder affecting blood coagulation is responsible for abnormal bleeding. Haemophilia A is the most common form of the disorder, being present in about 1 in 5,000–10,000 male births, while haemophilia B affects approximately 1 in 25,000 male births [1]. The etymological definition of haemophilia is “love of blood”. However, ironically, if you were to ask any patient with haemophilia (PWH) how they feel about the disorder, they would probably reply that their feelings towards blood are anything but loving!

Although brain haemorrhage and bleeding into internal organs represent major threats to the lives of PWH, approximately 80-90% of bleeding episodes occur in the musculoskeletal (MSK) system, especially in the large synovial joints (haemarthrosis), as well as in the muscles (haematoma), thus constituting the principal health problem. On account of the complex mechanisms to be examined later in this introduction in more depth, these recurrent haemarthroses induce progressive cartilage damage, leading to joint destruction and subsequent severe functional limitation. Therefore, even though haemophilia is a blood disease, the severity of its associated complications in the MSK system means that haemophilia is an orthopedic condition of great interest.

The two primary challenges of treating haemophilia are thus the treatment and, ideally, the prevention of MSK complications. The adequate prevention of MSK complications in PWH requires the early detection of the first signs of joint impairment in relatively asymptomatic patients as well as the efficient follow-up of MSK complications already present. Appropriate treatment, whether hemostatic or orthopedic, is only possible if we have reliable assessment tools at our disposal thus making it possible to quantify the benefits of such treatment. The aim of this PhD thesis is therefore to explore a new approach to the functional assessment of MSK complications in PWH by means of three-dimensional gait analysis (3DGA).

This thesis will therefore be of interest to haemophilia specialists interested in quantifying the joint damage of PWH as well as orthopedic specialists wanting to understand the biomechanical consequences of multiple joint impairments on gait pattern. A short introduction to haemophilia and blood-induced joint damage as well as some background on 3DGA are provided in this introduction, with the aim of familiarizing readers less familiar with one of these areas with the research domain of this thesis. As 3DGA is proposed as an innovative assessment tool in the case of haemophilia, it is therefore important to describe this tool and examine the existing ones, with regard to the recommendations of the World Health Organization (WHO). At the end of this chapter, the goals and research questions of this project are outlined.

Definition of haemophilia

Haemophilia is a rare hereditary coagulation disorder characterized by a deficiency or functional defect of either coagulation factor VIII in haemophilia A or factor IX in haemophilia B. The disease results from a defect in blood clot formation and is responsible for abnormal bleeding. PWH do not bleed more than individuals without haemophilia, but rather they bleed for longer. Haemophilia is an X-linked recessive disease, and so in principle, only males are affected. Haemophilia A and B are clinically similar and may be distinguished only by the assay of factor VIII and IX activity. The severity and frequency of bleeding in PWH is inversely related to the amount of residual factor VIII or IX in the bloodstream. Based on the residual activity levels of clotting factor VIII or IX, patients with "mild" haemophilia have levels of clotting factor between 6 and 24% of normal values and only develop bleeding complications after major trauma (Fig. 1). Haemophilia is defined as "moderate" when the clotting factor activity is between 2 and 5% of normal values, whereas patients with "severe" haemophilia have an activity level factor VIII or IX of less than 1%. "Severe" haemophilia affects approximately half of all patients and should be considered as a specific entity, since patients with severe disease experience repeated and spontaneous bleeding problems in the absence of adequate treatment.

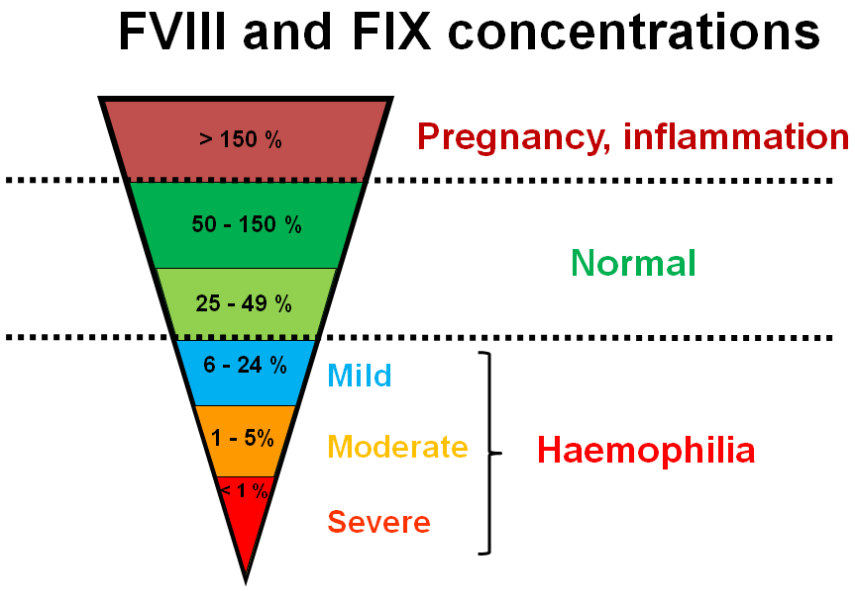

Fig. 1. Classification of haemophilia based on the activity levels of clotting factor VIII or IX

Preventive treatment of haemophilia is aimed at avoiding the consequences of bleeding episodes, especially, the joint damages resulting from repeated intra-articular bleedings. Inadequate or delayed treatment of acute haemarthrosis may trigger a series of pathological changes within the joint, leading to progressive arthropathy. The treatment of

haemophilia currently consists of replacing the missing clotting factor by intravenous injections, either by prophylaxis (long-term repeated injections on a regular basis, generally 2-3 times per week in order to prevent bleeding complications) or on-demand (episodic injections according to the patient's needs to treat or prevent a bleeding event) [2]. Therefore, the basic aim of regular factor replacement is to avoid joint bleeding or minimize joint injuries once repeated bleeding has occurred. Despite the availability of clotting factor, MSK impairment remains an issue of great concern, as the majority of PWH worldwide has limited access to clotting factor concentrates. Generally, in developed countries, such as Western Europe and the United States, clotting factor is readily available, but this is not the case worldwide. It is estimated that approximately 80% of patients do not receive proper treatment, *i.e.*, they are "on-demand" or even untreated, because of financial constraints limiting the access to and use of factor concentrates [3].

Without prophylaxis, recurrent haemarthroses occur at a very early age, as early as 2 years, when the child begins to walk. The majority of patients with severe haemophilia experience haemarthrosis between the ages of 2–5 years and develop arthropathy during the second or third decades of their lives [2]. In severe cases and in the absence of treatment, PWH may suffer up to 30–35 haemarthroses per year [4]. The pathogenesis of the progression from recurrent haemarthrosis to haemophilic arthropathy, particularly in the early stages, will be henceforth detailed.

Musculoskeletal complications in haemophilia: from the acute bleed to the target joint

Although prophylactic treatment significantly reduces the occurrence of acute bleeding, it does not completely stop its occurrence. About 90% of people with severe haemophilia experience chronic degenerative changes in joints by the second or third decade of their lives [5]. It remains unknown how many haemorrhages into a joint are necessary before irreversible progressive cartilage and joint destruction take place, but it is likely that only a small number is needed to initiate the pathological process [6]. The pathogenetic mechanism of haemophilic arthropathy is considered to be multifactorial, involving changes in the synovial tissue, cartilage, and subchondral bone. The repetition of haemarthroses leads to haemophilic arthropathy and the development of a so-called "target joint". A target joint is known as a joint that has been affected repeatedly by bleeding and thus, become more susceptible to subsequent bleeding.

The key event in the development of haemophilic arthropathy is the presence of blood in the joint [7;8]. The origin of this intra-articular bleeding is the synovial membrane, or more specifically, the subsynovial plexus. Synovial tissue has the function of removing the waste – including blood - from the synovial cavity. After a small number of haemarthroses, a

state of hypertrophic synovitis occurs, as the synovium is unable to reabsorb the excessive quantity of blood within the joint. The iron contained in the hemosiderin (the breakdown product of hemoglobin) accumulates in the synovial tissue (Fig. 2A), and its deposit causes a marked inflammatory response in the synovium. Haemarthrosis also leads to synovial hypertrophy, hypervascularization, and cartilage damage (Fig. 2B and Fig. 3A) owing to chondrocyte apoptosis, which gradually but inevitably ends up destroying the joint [9]. In addition, blood has a direct and harmful effect on cartilage, which may even develop before the synovial inflammation [10]. The prolonged effects of exposing the cartilage to blood are due to the apoptosis of the chondrocytes, which are the cells responsible for producing and maintaining the cartilage matrix. In summary, when taken together, haemarthroses lead to inflammatory changes in the synovial tissue as well as degenerative changes in the cartilage.

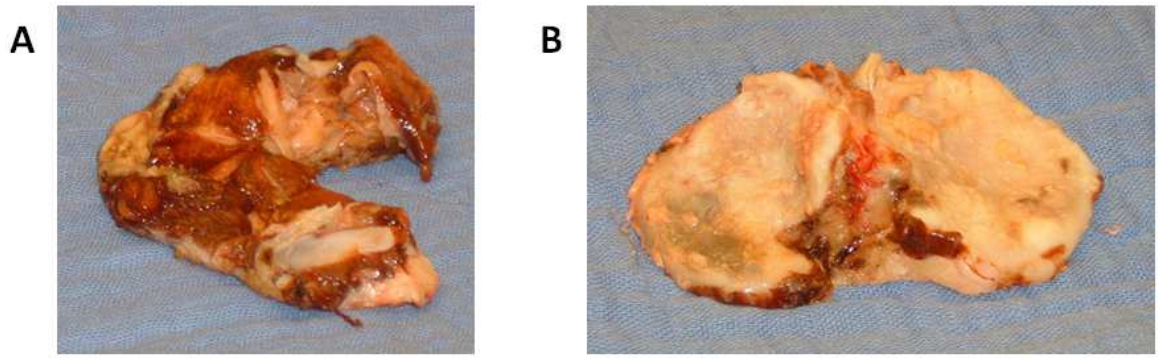

Fig. 2. Perioperative pictures of a total knee replacement in a patient with severe haemophilia. The images show the iron deposition accumulated in the synovial tissue (A) and the end-stage cartilage damage caused by repeated bleeding (B)

Knees, elbows, and ankles tend to be the most severely involved joints, accounting for 80% of haemarthroses in PWH [9]. The hip, shoulder, and wrist are much more rarely affected, while smaller joints only bleed occasionally. It is not known why some joints are more commonly affected than others, although it has been suggested that this could be related to biomechanical factors and inadvertent microtrauma [11]. It is the large synovial surfaces and rotation forces characteristic of the knee, elbow, and ankle, which may cause these joints to bleed [9]. Some patients have such severe arthropathy that orthopedic surgical procedures are required, such as joint replacements (Fig. 3B) and joint fusions (arthrodesis).

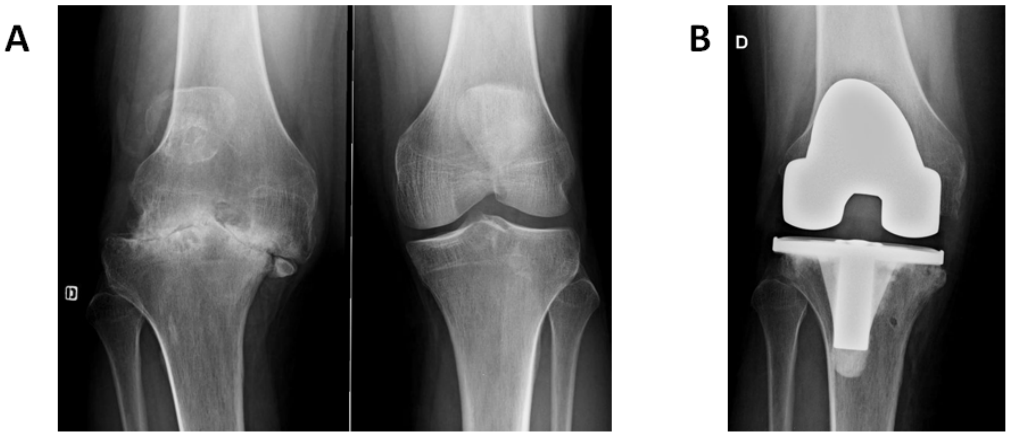

Fig. 3. End-stage arthropathy of the right knee in a 32-year-old patient with severe haemophilia A (A left) who has experienced bleeding episodes since childhood. For the same patient, structural aspect of the left knee (A right) that had never bled should be compared. This patient underwent a total knee replacement of his right knee (B)

Finally, even if the joints are most commonly involved, recurrent and non-resolving soft-tissue bleeding may also occur, leading to arthrofibrosis and subsequent joint stiffness [12]. Due to the presence of associated bone deformities, approximately 50% of patients with severe haemophilia develop joint contractures and angular deformities exceeding 10° [5;9;13] (Fig. 4). These contractures may result from recurrent haemarthrosis with subsequent fibroblastic proliferation and progressive arthropathy, or from extra-articular intramuscular bleeding leading to fibrosis [14]. In severe cases, intramuscular haematoma may also cause severe neurological complications, such as femoral nerve palsy following iliopsoas haematoma or compartment syndrome of the forearm (Volkman syndrome) [15].

In summary, contrary to osteoarthritis (OA), which is generally limited to an isolated joint, haemophilia destroys joint cartilage in multiple joints concomitantly and leads to severe vicious posture due to muscle fibrosis.

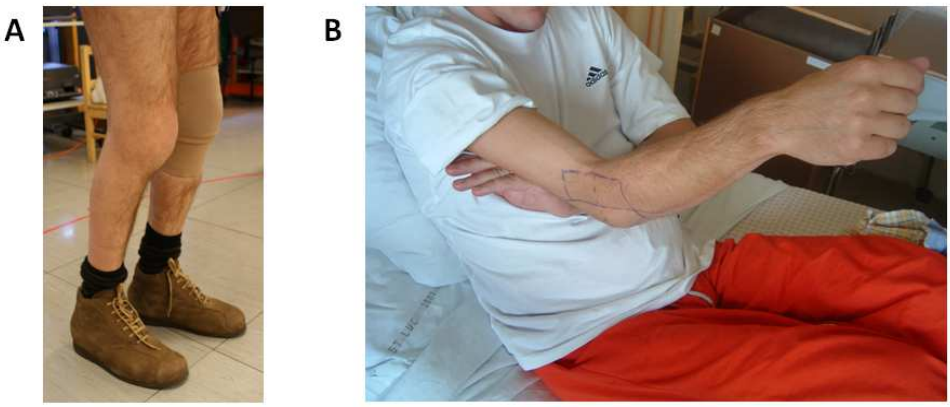

Fig. 4. Bilateral knee flexion contracture (A) due to severe arthropathy of the right knee (note the presence of the swollen aspect of the joint due to chronic synovitis), which persisted after unilateral total knee replacement of the left knee. (B) Flexion contracture of the right elbow prior the placement of a total elbow prosthesis

Assessment of MSK complications of haemophilia in the light of the International Classification of Functioning, Disability, and Health

In addition to the structural damage to joint cartilage by recurrent bleeding episodes, functional limitations as well as difficulties in performing and participating in daily activities may be experienced by PWH. The functioning of a subject is therefore described from the perspective of the body, individual, and society by the International Classification of Functioning, Disability, and Health (ICF) proposed by the WHO in 2001 [16]. Over the last decade, the ICF model has gained worldwide acceptance among health researchers and practitioners as a framework to be used to support a systematic approach for understanding chronic illness and disability across diverse populations and cultures [16]. The aim of the ICF is to provide a common language in all health domains for clinical practice, teaching, and research.

The ICF is organized in two parts: “functioning and disability” concern the components of “body functions and structures” and “activities and participation”, whereas “contextual factors” relate to “environmental factors” and “personal factors (Fig. 1, chapter 1). As the “body functions and structures” and “activity” components are addressed in the thesis, I will first describe the model in its entirety in order to better understand the impact of MSK comorbidities in PWH and clarify the ICF components commonly used in haemophilia-specific assessments. So as to be as relevant as possible, the ICF model will be described from the perspective of a PWH suffering from a severe knee arthropathy.

ICF model applied to haemophilia

The major complications experienced by haemophilia patients (“health disorder”) are recurrent bleeding episodes, which may affect the “**body structures”**. “Body structures” are body parts, such as organs, limbs, joints, and their components (*e.g.*, muscles, ligaments). The impact of haemophilia on body structures is quite obvious, since recurrent bleeding episodes induce, among other things, cartilage loss, gradual bone changes, deformities, and muscular atrophy [9]. Moreover, haemophilia may also affect several “**body functions”**. “Body functions” are defined as the physiological functions of these systems. Impaired motor functions in a patient suffering from severe knee arthropathy are principally manifest as a reduction in the passive and active range of motion (ROM), muscle strength, and proprioception. The “body function and structure” domain in PWH is currently assessed using clinical and radiological scores. As 3DGA is intended to focus specifically on functional assessment, “body function and structure” need to be discussed in more detail.

Haemophilic arthropathy may also limit carrying out activities, leading to disability. **“Activities”** involve performing tasks or actions, which may be performed by the individual

[16]. In our example, these limitations refer to an inability in executing tasks that require the lower limbs (*e.g.*, throwing a ball, running, climbing stairs). Activity limitation can be measured using two haemophilia-specific scores: a self-report score, the Haemophilia Activities List (HAL) [17], and performance-based score, the Functional Independence Score for Haemophilia [18;19].

Finally, haemophilia may restrict the patient's participation in everyday life. **"Participation"** is defined as an involvement in social situations, such as sports, work, leisure, or social events [16]. Restricted participation concerns the problems experienced by the patient in the fulfillment of social roles, which are regarded as normal for their age, society, and culture [20]. For instance, participation restrictions may include difficulties in caring for their children, gardening, visiting a museum, or going to the cinema. At present, no specific suggestions have been proposed with regard to the evaluation of the restrictions in the "participation" area for PWH [21].

Functioning and health are not only associated with the underlying disease, but they are also influenced by **"contextual factors"** relating to a person's background, which include both "environmental factors" and "personal factors". **"Environmental factors"** consist of the physical, social, and attitudinal environment in which the patient lives and conducts their day-to-day activities. These include the positive or negative attitude of their family, colleagues, and neighbors, as well as the architectural barriers faced by a patient with impaired mobility and need for technical aid. **"Personal factors"** involve the patient's characteristics, which are not part of the health condition (*i.e.*, age, lifestyle, habits, motivation, personality, and social background). Environmental and personal factors may facilitate or hinder the patient's functioning. For instance, poor motivation may prevent the patient from receiving physiotherapy, while fear of attitudinal behavior may restrict the patient's participation. On the other hand, the use of assistive devices may reduce activity limitation.

How to explore ICF's body structure and function in haemophilia?

In haemophilia, the evaluation of the "body function and structure" component should take account of the wide spectrum of severity in haemophilic arthropathy, which ranges from small or absent joint damage in young children on prophylaxis to severe disabling arthropathy in poorly or inefficiently treated patients. With respect to haemophilia, the "body function and structure" area has traditionally been evaluated using both radiological and clinical joint scoring systems. Information obtained from these scores is regularly used in clinical practice to evaluate the effects of different treatments on the progression of arthropathy, including clotting factor prophylaxis, physical therapy, and surgical procedures [22]. As one aspect of this thesis is the comparison of 3DGA with existing

methods for joint assessment in PWH, it is therefore important to first describe these assessment tools.

Radiography has been used for several decades to evaluate and gauge haemophilic arthropathy. Two classification systems based on conventional radiography of the ankles, knees, and elbows have widely been used to quantify haemophilic arthropathy in clinical trials, namely the *Arnold–Hilgartner (A-H) scale*[23] and *Pettersson score* [24]. The *A-H scale* was described in 1977 and is a progressive scale in 6 stages (stage 0-5). The worst findings reflect the end-stage arthropathy (stage 5). The *A-H scale* is based for the most part on the roentgenographic findings and attempts to separate the joint changes into stages that have surgical significance. The *Pettersson score* is an additive scale, with each abnormality graded from 0 to 1 or 2, which are then summed up in order to obtain an individual joint score (Fig. 5). There are differences between the two scoring systems. The *A-H Scale*is simple and easy to use by everyone. The *Pettersson score* is more meticulous, but discriminates better between different stages of haemophilic arthropathy. In addition, the *Pettersson score*does not attempt to evaluate soft-tissue changes as these are inherently difficult to assess on plain radiography. The major limitation of radiography is that it only visualizes gross joint alterations, but cannot detect early change in soft tissues, synovium, or cartilage, meaning that radiography is insensitive to the early changes of haemophilic arthropathy [25]. Thus, once radiographic changes are observed, the clinical course of arthropathy is usually at an advanced and irreversible stage. Improved therapy has consequently led to the need for more refined and sensitive tools to monitor subtle changes in joints.

Type of Change	Finding	Score
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral surface	Absent	0
	Partially involved	1
	Totally involved	2
Narrowing of joint space	Absent	0
	Joint space >1 mm	1
	Joint space <1 mm	2
Subchondral cyst formation	Absent	0
	1 cyst	1
	>1 cyst	2
Erosions of joint margins	Absent	0
	Present	1
Gross incongruence of articulating bone ends	Absent	0
	Slight	1
	Pronounced	2
Joint deformity (angulation and/or displacement between articulating bones)	Absent	0
	Slight	1
	Pronounced	2
Possible joint score		*0–13*

Fig. 5. World Federation of Haemophilia Pettersson scale of haemophilic arthropathy

Fig. 6. Radiographic Pettersson score for the left (A) and right (A bis) ankle of a 27-year-old patient with severe haemophilia A. The highest score for an individual joint is 13, which indicates a totally destroyed joint. (B) End-stage ankle arthropathy (avascular necrosis of the talar dome, multiple osteophytes, joint-space narrowing, irregularity, and bone cysts) in a 57-year-old patient with haemophilia A

Ultrasonography (US) is a low-cost, non-invasive, and real-time technique [26;27]. US is ideal for determining the extent and degree of soft-tissue inflammation, detecting the presence of intra-articular fluid, carrying out follow-up, and fine tuning treatment in patients with haemarthrosis or chronic synovitis [28].

Magnetic resonance imaging (MRI) is currently the most sensitive imaging technique for the early detection of joint lesions [29] (Fig. 7). In contrast to conventional radiography and US, MRI offers multitissue imaging, involving the bones as well as the surrounding ligaments and tendons. MRI is therefore capable of revealing all the lesions characterizing haemophilic arthropathy and may be used to detect and monitor less advanced joint damage, which is particularly seen in patients in the early stages of arthropathy. MRI is therefore considered the gold standard for identifying early change in joints. Nonetheless, MRI is costly, less accessible, and more time consuming than other imaging techniques. Furthermore, it often requires sedation in children.

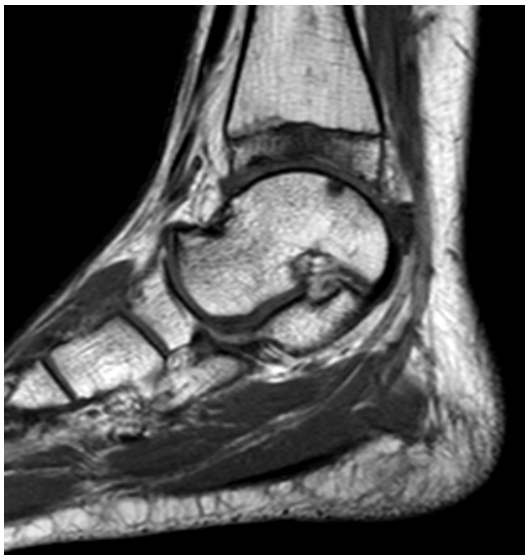

Fig. 7. MRI: early stage of arthropathy in a 15 year-old boy with severe haemophilia A. Sagittal T1-weighted sequence showing sub-chondral bone irregularities and oedemas in tibia and talar dome,

Clinical scoring systems have been used at a number of haemophilia treatment centers as a part of routine clinical follow-up as well as in some of the major studies on prophylaxis in which orthopedic outcomes were assessed. Whereas radiography, US, and MRI only provide knowledge about the anatomical structure of the joints, *i.e.*, the “body structure” component, the *WFH (or Gilbert) score*[30] (Fig. 8) is an additive score based on seven components, including both the “body function” (joint ROM, presence of flexion contracture, and joint instability) and “body structure” (presence of swelling, muscle atrophy, axial deformity, and crepitus with motion) of the major joints affected by haemophilia. Similarly to radiographic scores, the WFH score was developed at a time when

few patients underwent prophylaxis. The WFH score is therefore insensitive to early clinical manifestations. The *Hemophilia Joint Health Score (HJHS)*[31], recently developed by a consensus of experts, is more sensitive to early changes, and while originally created for a pediatric population, this score may also be used in adults.

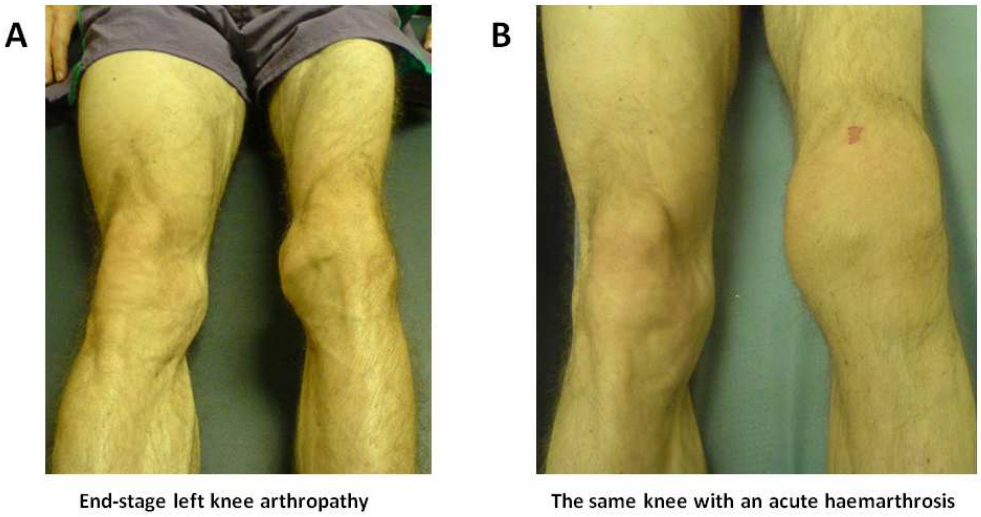

Fig. 8. Patient with a severe arthropathy of the left knee (A). The WFH clinical score is 8/12 because of the presence of flexion deformity, severe limitation in flexion, severe muscle atrophy, crepitus on motion, and instability. The clinical score cannot be performed when the patient presents acute joint bleeding (B)

3DGA as a new tool to explore the functional impairments in haemophilia?

In patients suffering from knee OA, several authors [32;33] have already noted discrepancies between some of the structural changes in the joint detected using X-rays and the clinical manifestation of the disease, such as pain and functional disability. In 1992, Hadler [34] observed in an article entitled “Knee pain is the malady—not osteoarthritis” that “The epidemiology of osteoarthritis and the epidemiology of pain have little in common, not nothing in common, but surprisingly little.” With regard to PWH in particular, Rodriguez-Merchan [13] described the phenomenon of haemophilic joints, which, despite appearing severely destroyed on X-rays, seem to continue functioning well over many years. Hamel *et al.*[35] reported the case of an 18 year-old haemophilia patient presenting a preserved clinical score (painful joint with only moderate impairment of ROM), but with a significantly affected radiological score (flattening of the talus with advanced arthritic changes). Similarly, Den Uijl *et al.*[36] recently reported a low correlation between MRI and clinical function as assessed by the HJHS. This is corroborated by the findings of Pergantou *et al.*[37] who reported 50% discordance between the clinical WFH joint score and MRI.

In haemophilia care, the assessment of the lower limb joints is therefore of paramount importance for the diagnosis of haemophilic arthropathy, treatment initiation,

prevention of disease progression, and comparison of treatment strategies, such as prophylaxis. Given this context, **3DGA is an approach designed to focus exclusively on the "body function" component of the joint** (kinematic and kinetic) **or whole body** using the global gaitfunction(mechanic and metabolic measurements). Moreover, contrary to radiological and clinical examinations performed in a supine position, the uniqueness of 3DGA is that it assesses the patient during the act of walking, *i.e.*, under weight-bearing conditions. This is of the utmost importance, as pain induced by weight-bearing activities influences the functional performance of the arthropathic joints significantly.

With this research project, the Haemophilia Center of the *Cliniques Universitaires Saint-Luc* (Prof. C. Hermans, Dr C. Lambert, and Prof. C. Vermylen) has collaborated with the Clinical Gait Analysis Laboratory (Prof. C. Detrembleur) and "diabetic foot" consultation (Dr L. Haenecour) of the Rehabilitation Medicine Unit in order to provide an integrated haemophilia joint assessment clinic. The overall aim of such an institute is to provide up-to-date expertise in the diagnosis and prevention of intra-articular bleeding and combine prophylactic replacement therapy with a state-of-the-art orthopedic approach.

Instrumented 3DGA

Biomechanics applies the laws of mechanics to living structures, such as the locomotor system. The term gait analysis has several meanings, ranging from a brief observation to sophisticated computerized measurements. Observational gait analysis is limited because it cannot determine the biomechanical causes of an abnormal gait. Part of the problem with walking is that the action is done so effortlessly and subconsciously that it is difficult to appreciate the immense complexity involved. In 3DGA, biomechanics analysis tools are used to unravel the mechanics of gait and pinpoint which joint or muscle system is responsible for the functional deficit so that appropriate interventions may be initiated. The methodology of this thesis uses an instrumented 3DGA approach to underline the biomechanical consequences of the various lower limb arthropathies in PWH by quantifying joint kinematics, kinetics, spatiotemporal parameters, mechanical work, and metabolic variables.

Kinematics

A digital video-based motion analysis system analyzes the **kinematic** part of locomotion. Kinematic analysis measures the active ROM of a joint. For this 3DGA study, our laboratory is currently using a motor-driven treadmill (Fig. 9A), as it has the advantage of being safe (with a harness supporting the patient in case of fall) and requiring less space, while the walking speed may be directly controlled. While the patient is walking on the

treadmill, a system composed of six infrared cameras tracks and records the trajectories of passive reflective markers (typically small spheres covered with reflective tape) positioned on the skin in relation to anatomical or bony landmarks to define body segments (Fig. 9A and 10). In gait analysis, body segments (*i.e.*, foot, shank, thigh, and trunk) are defined as a straight line between two markers, usually considered as rigid structures that may be represented by sticks. Although the soft tissue around the body segments is deformable due to skin layers and muscle tissue, the body segments are considered to be rigid in gait analysis, with this deformability being ignored. If two or more cameras detect a marker, then it is possible to calculate the 3D trajectory of that marker (Fig. 9B). Joint angles are calculated from the changing orientation of the observed body segments (Fig. 9C). Joint angles describe the angle between two adjacent segments in a particular anatomical plane (sagittal for flexion/extension movements, frontal for abduction/adduction movements, and transverse for internal/external rotation).

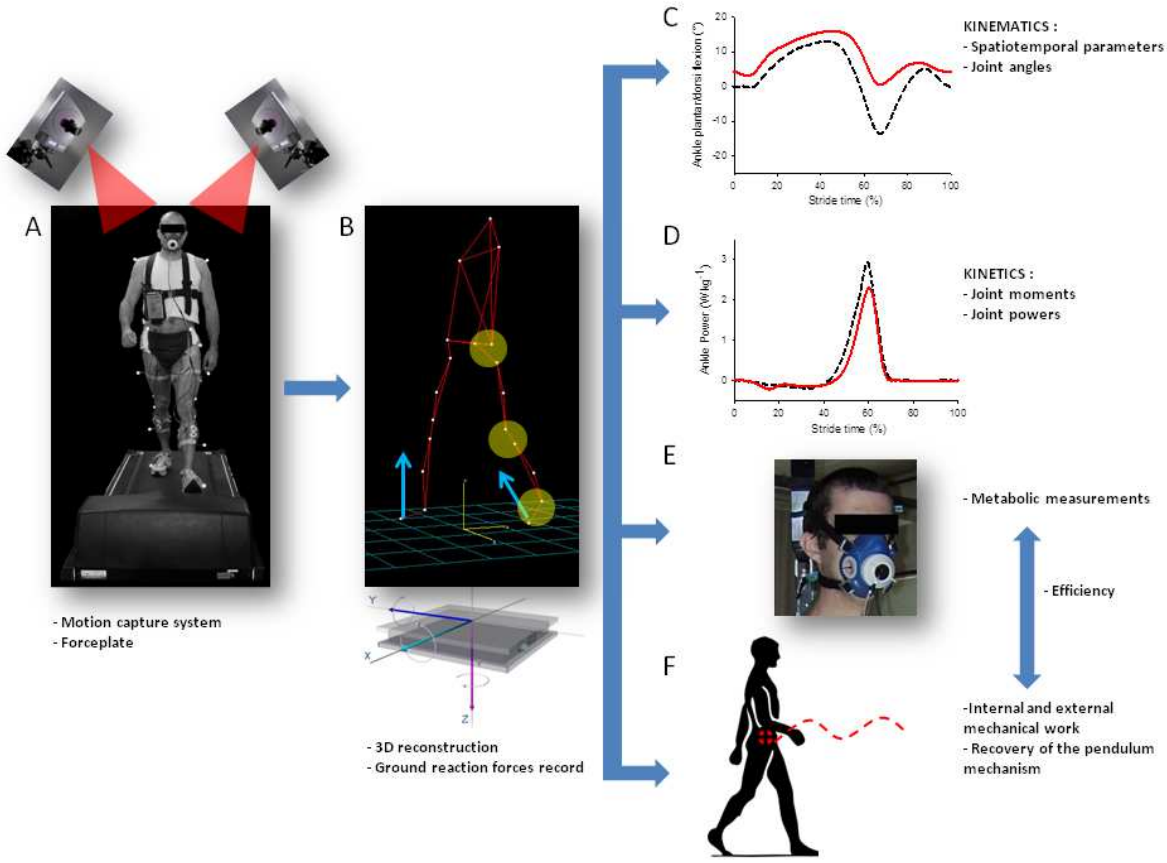

Fig. 9. The infra-red cameras (A) are positioned so that at least two visualize each marker at any given time. Powerful infra-red light sources around each camera reflect from the reflective markers and result in a corresponding bright spot in each image, with these spots then being reconstructed to generate the 3D trajectories (B). The images are then processed to derive the graphs of the kinematics (C). The joint ROM can be quantified, plotted, and compared with age-specific normal values. A force platform located under the treadmill (B) records patient's ground reaction forces. The joint moments and powers, *i.e.*, kinetic data (D) are derived from force platform measurements and kinematic data. Energy expenditure is measured indirectly based on the rate of oxygen consumption by the patient using an ergospirometer (E). Finally, the mechanical work is calculated as the work performed to raise and accelerate the center of body mass (F) and exerted by muscles to move the body segments relative to the center of body mass. The EMG was collected but not used in this study.

In our protocol, the kinematic model of Davis [38] was used (Fig. 10). The hip was modeled as a ball and socket joint, *i.e.*, it could move in the three anatomical planes. Usually, the model of Davis depicts the knee in three planes, but because of a lack of reproducibility, the frontal and transverse planes were abandoned and instead, the knee was modeled as a hinge joint that can only move in the sagittal plane. The ankle was recorded in the sagittal and transverse planes. The movements of the ankle in the frontal plane (pronation/supination movement) as well as the movements in the midfoot and forefoot are also of great interest, but they concern the limited amplitude of movement involving relatively small bones. The precision of our general kinematic model did not allow for such a comparison, although this could be approached in the future using specific kinematic models of the foot [39].

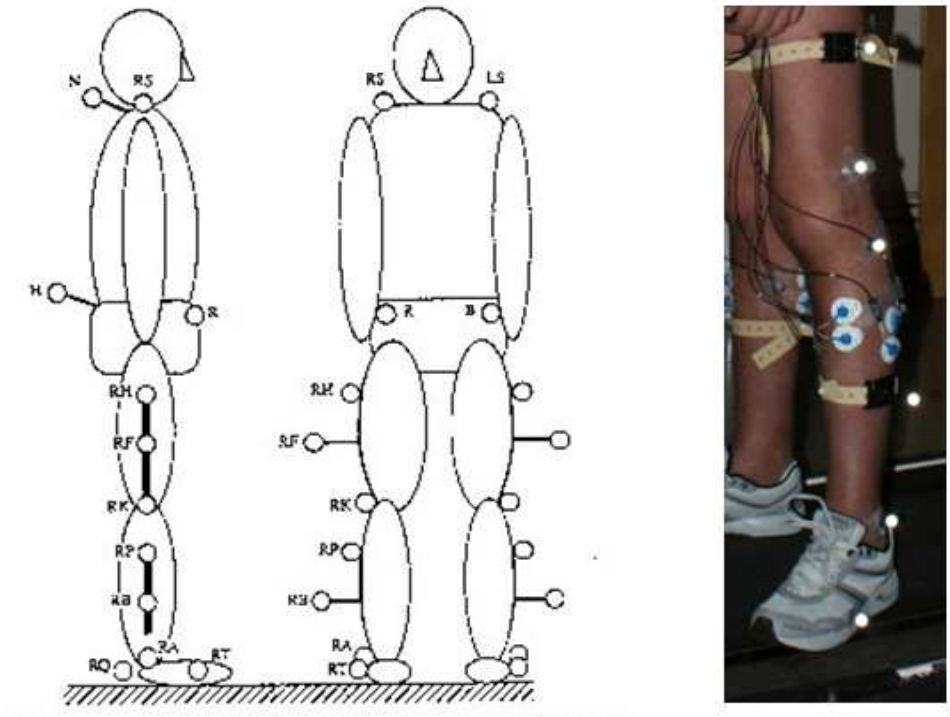

Fig. 10. Reflective markers are positioned on the patient's body according the kinematic model of Davis *et al.*[38]. . The EMG was collected but not used in this study.

In addition to the standard 'absolute angle' calculation, subtraction of an 'offset' by the corresponding static posture angle was performed on all joints. The subtraction of the offset by static posture angles from joint movements is an option sometimes adopted, aimed at removing the bias associated to anatomical frame definitions. Absolute angles represent well what is directly observed, but bone or joint deformities as well as conservative interventions such as orthopaedic shoes (as proposed in chapter 5) will result in walking patterns that cannot be compared with each other. After a static offset subtraction, Leardini *et al.*[46] found the inter subject variability to be reduced in most of kinematic variables.

Spatiotemporal parameters may also be assessed using the 3D position markers. Gait may be characterized by a cyclical movement and periods of loading (stance phase) and unloading (swing phase) of the lower limbs. By convention, the gait cycle equals one stride and contains a sequence of events that usually begins with floor contact (0%) with one foot and ends with the next contact of the same foot (100%), which corresponds to the initial contact of the next cycle (Fig. 11). Therefore, one stride is made up of two steps. In a normal symmetrical gait, the stance phase typically accounts for 60% of the gait cycle, while swing represents the remaining 40%. There is some overlap between the stance phases of the right and left gait cycle. The period during which both feet are in contact with the ground is called the double support (contact) phase, which lasts for about 10% of the gait cycle and occurs twice during each cycle. These functional measurements, which provide valuable clinical information about the patient's movement patterns, include cadence, step length, and the percentage of stance-phase and swing-phase duration.

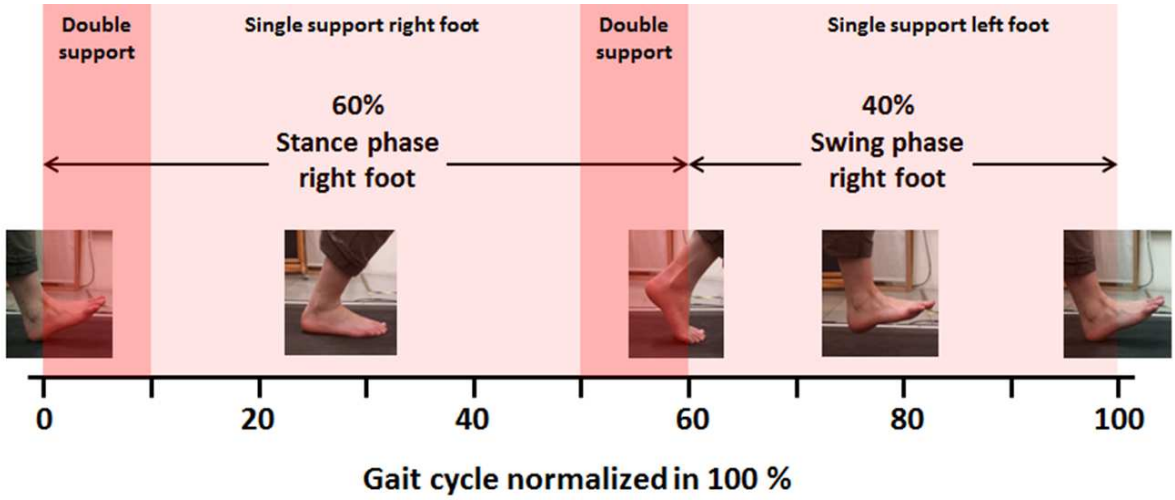

Fig. 11. A complete gait cycle is defined as the movement from one foot strike to the successive foot strike on the same side (right foot on these pictures). In this study, gait cycle will be normalized in percentages and used as the abscissa of the kinematic (*e.g.*, foot kinematics in this example) and kinetic variables

Kinetics

Kinetics is defined as the characterization of forces, which act upon the body segments resulting in movement. Studying the kinetics of the lower limbs is possible by synchronizing a force platform with the motion analysis system. To calculate kinetics, the masses of the limb segments need to be known, and the location of their center of gravity has to be calculated using the table of anthropometry. A force platform composed of four 3D strain-gauge force transducers located under the treadmill simultaneously measures the ground reaction forces (GRF) generated by the body in three directions: vertical, lateral, and forward (Fig. 12). Gravity causes us to exert a certain force on the earth; which in turn exerts

an opposite and equal force; the force platform converts these forces into electric signals. See Appendix 1 for details on GRF decomposition with the treadmill forceplate.

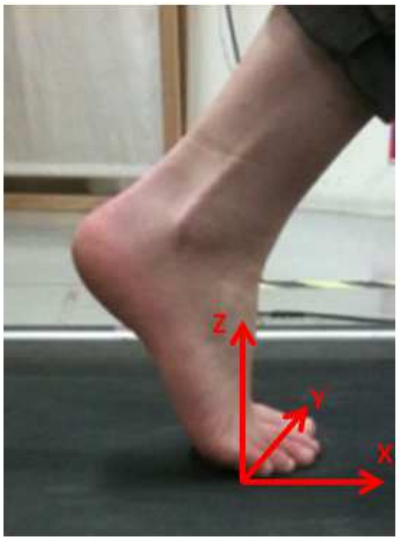

Fig. 12. A force platform located under the treadmill simultaneously measures the ground reaction forces generated by the body in three directions: vertical (Z), lateral (Y), and forward (X). The point of application of the ground reaction force is found underneath the contact foot and is directed opposite to the body weight

Taking direct measurements of muscle forces is not practical, as they require invasive procedures. To obtain kinetic values, such as the net moments of force and power generated or absorbed at the major joint muscles in the sagittal plane, the mathematical approach of inverse dynamics is used. This approach is based on Newton's equations [40] and involves working back from the kinematics to deduce the muscle force that must be responsible for it.

If both the GRF and joint angle excursions are known, the net **joint moments** may be calculated. Net joint moments are the net result of muscular and non-muscular forces (such as tension from ligaments and joint capsule) acting around a joint and causing movement in this particular joint. Net joint moments categorize the type of movement generated by dominant muscles (*i.e.*, plantar or dorsiflexion moment of the ankle, bending or stretching moment of the knee). See Appendix 6 for details on joint moment estimation by inverse dynamics.

Inverse dynamic analysis also allows one to determine the rate at which energy is delivered by the muscles moving a certain joint by calculating the **joint power** output (Fig. 9D). So-called joint power is related to the type of muscle contraction and is a measure of how much effort it takes to perform a specific movement. Net positive power is typically associated with concentric muscle contraction (*e.g.*, a flexor muscle contracts while the joint is flexing), whereas net negative power refers to eccentric muscle contraction (*e.g.*, a flexor muscle contracts while the joint is extending in order to decelerate the limb). Joint power is defined as the product of the angular velocity of the joint and net joint moment. Angular velocity is the time derivative of angular displacement, which means that joint power is indirectly influenced by joint ROM.

Energetic and mechanical work production

Kinematics and kinetics tend to document disease consequences at a single joint level, without reflecting the impact on the body as a whole. The gait laboratory at the *Cliniques Universitaires Saint-Luc* specifically aims to evaluate the repercussions of segmental abnormalities on global body function by calculating more "general" indices, such as mechanical work and metabolic measurements. Contrary to kinematics and kinetics data, which are specific to each of the individual lower limb joints, "general" indices are unique to each patient and therefore likely to be more relevant in the objective assessment of patients' problems in performing basic tasks, such as walking.

The main disadvantage of gait abnormalities from any cause is that they force the patient to expend more energy for the same effort as compared to normal individuals [41]. **Energetics** refers to the measurement of energy use, such as the total chemical energy used by the muscles to perform exercises [42]. Energy expenditure is measured indirectly based on the rate of oxygen consumption by the individual (VO_2) using an ergospirometer (Fig. 9E). The net metabolic cost (C_{net}) (*i.e.*, the energy produced by the muscles per unit of distance) is calculated as the net oxygen consumption over walking speed. The goals of achieving a normal gait are not only to decrease the stress on the muscles and joints, but more importantly, to decrease the energy required to move from place to place [42]. See Appendix 2 for details on measurements of the energy consumption during walking.

Mechanics defines the total mechanical work (W_{tot}), which is calculated as the sum of the external work (W_{ext}) and internal work (W_{int}) (Fig. 9F). W_{ext} is the mechanical work performed to raise and accelerate the center of body mass (CoM) relative to the surroundings. Computing GRF allows the potential and kinetic variations of the CoM displacements to be evaluated by successive integration. The sum of the increments of energy calculated on the total external energy curve corresponds to the W_{ext}. The W_{int} includes the work performed by the muscles to move the body segments relative to the CoM and the work done by the lower limbs moving against each other during the double stance phase ($W_{int,dc}$), in addition to the work to overcome internal friction and sustain co-contractions. Only the two first aspects are measurable, although $W_{int,dc}$ was not taken into account in this thesis as it requires recording the GRF of both lower limbs on two different force platforms, which was not possible with our treadmill. In terms of kinematics, computing angular and linear speeds of the body segments relative to the CoM allows the kinetic energy variation of each body segment relative to the CoM to be evaluated. The sum of increments of energy calculated on each curve of kinetic energy for each body segment corresponds to W_{int}. See Appendix 3 and 4 for details on the calculation of internal and external mechanical work.

One approach of combining the data obtained by energetic (what is consumed) and mechanical work (what is produced) is to calculate the **efficiency** of the positive mechanical

work production of walking. Efficiency represents the percentage of metabolic energy actually transformed into mechanical energy by the muscles, and it is calculated as the ratio of W_{tot} to C_{net}.

In walking, the CoM (located approximately just above and between the hip joints) is lifted up and down during the stride (Fig. 13). The pathway of the CoM is a smooth, regular curve that moves up and down in the sagittal plane with an average rise and fall of about 3-4 cm at a spontaneous speed of 4 km h^{-1}. The CoM reaches its highest position during mid-stance and its lowest position during the double contact phase (Fig. 13), while it accelerates and decelerates successively during the stride. This vertical movement occurs once with each step and enables individuals to save energy, because we slow down as we rise and speed up as we fall, thus passively recovering kinetic energy as gravitational potential energy and back again, as in an inverted pendulum. The **recovery** index is indicative of the efficacy of this gait mechanism. At preferred walking speed, as much as 60-65% of the required external mechanical energy may be recovered owing to this energy saving mechanism [43]. The other 35-40% of external mechanical energy is lost from the system and must be supplied by the muscles. This pendulum-like mode of walking reduces the mechanical work actively supplied by the muscles to walking and thus, it is supposed to save metabolic energy. See Appendix 5 for details on the calculation of the recovery index.

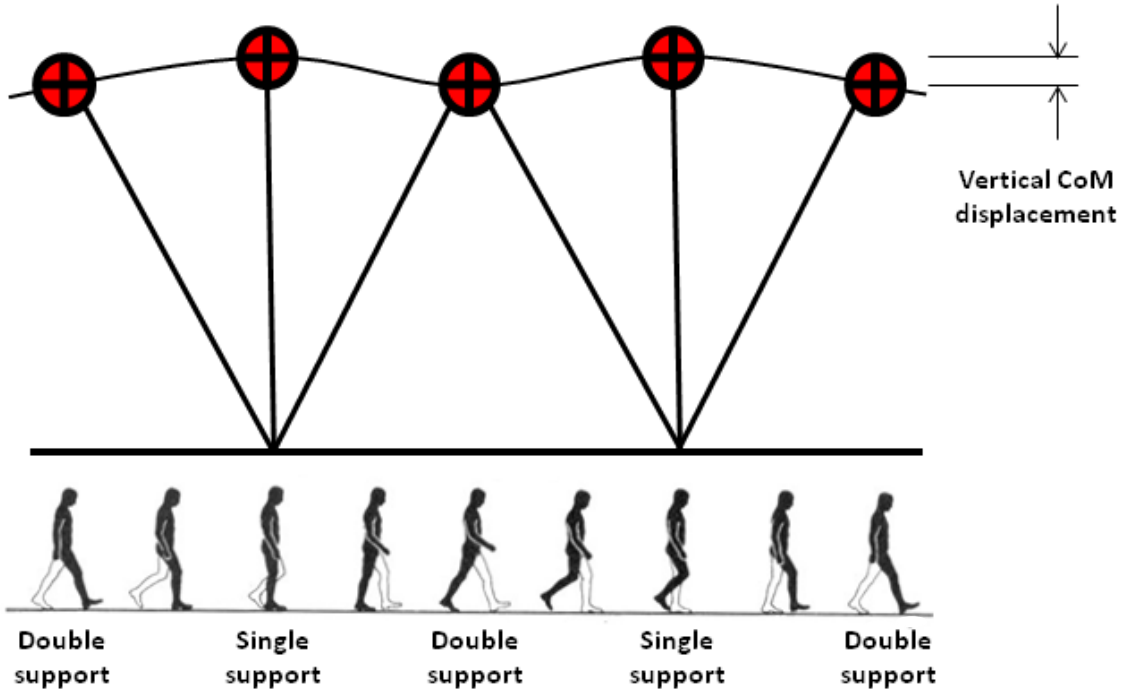

Fig. 13. Inverted pendulum model of gait, showing how the center of body mass (CoM) rises during the single support and falls during the double support

Outline of the thesis

The aim of this thesis is to evaluate whether 3DGA provides an innovative instrument for the functional assessment of PWH. The thesis also endeavors to improve our knowledge of the biomechanical consequences of haemophilic arthropathy on gait pattern using 3DGA. Finally, this method is tested as an assessment tool in the context of a clinical study.

Section 1: Pathophysiology of gait in patients with haemophilia

In order to determine the scientific credibility of 3DGA in assessing function, some of the psychometric properties of 3DGA are evaluated in the first two chapters. As previously reported, discrepancies between the structure and function of a knee with OA are found in the general population. As no instruments are available to measure joint function in PWH, 3DGA is proposed for this purpose. Using haemophilic ankle arthropathy as an example, **chapter 1** therefore aims to explore this relationship specifically in the case of the ankle joint of PWH by comparing the commonly used radiological scores, clinical scores, and the most representative 3DGA variables of ankle function. For this purpose, comparison of kinematic and kinetic parameters of the ankle with a validated OA functional outcome measure (Revised Foot Function Index Short Form) will be performed.

In **Chapter 2**, the test-retest reproducibility of 3DGA is assessed. For this, the MSK function in PWH was hypothesized to be relatively stable over a short period of time. In this setting, 18 adults with established haemophilic arthropathies were evaluated twice using 3DGA, with a hierarchy of the most reliable 3DGA variables being established. This repetitive assessment design allows the natural progression of haemophilic arthopathy to be assessed, thus giving some indication about the capacity of responsiveness (sensitivity to change) of 3DGA, *i.e.*, its power to detect a difference in time when one exists.

In the context of understanding the impact of functional alterations caused by multiple lower limb joint impairments, PWH are unique, as they usually suffer from various severe arthropathies and/or have undergone orthopedic surgical procedures. The purpose of the study developed in **chapter 3** is thus to observe the metabolic cost, mechanical work, and efficiency of walking among PWH and to compare the results with speed-matched values in healthy control subjects. The relationship between the extent of joint damage and the observed changes in mechanical and energetic variables is also investigated.

Section 2: Haemophilic ankle arthropathy

Advances in replacement therapy have resulted in reduced bleeding frequency and the preservation of almost clinically normal joints in PWH. However, the ankle joint seems to be an exception to the rule, since PWH still have the onset of ankle arthropathy despite regular prophylaxis (Fig. 14). As a consequence, the ankle is now the main joint affected in patients under 20 years of age suffering from severe haemophilia [45]. Additionally, although it is widely accepted that ankle OA affects patients' locomotion, no published data has described the effects of ankle arthropathy on gait pattern. **Chapter 4** intended to isolate PWH with only ankle impairments in order to observe the biomechanical impact of unilateral and bilateral ankle OA on the mechanical and energetic aspects of gait as well as the possible compensation of other lower limb joints.

Contrary to severe hip and knee haemophilic arthropathy, wherein joint replacement is the gold standard of treatment, the consensual approach of ankle OA in PWH is based on surgical procedures, such as fusion (arthrodesis) of the tibio-talar and/or sub-talar joint. Currently, there are no validated conservative options for managing haemophilic ankle arthropathy. While the feasibility, technical aspects, and results of foot orthoses have been widely studied in other foot and ankle conditions (*e.g.*, rheumatoid arthritis and diabetic foot neuropathy), no study has yet addressed the potential benefits and practicalities of foot orthoses in moderate and end-stage ankle haemophilic arthropathy. In **chapter 5**, the effects of custom-made orthopedic innersoles and shoes are experimentally investigated in PWH presenting ankle arthropathy, with special attention given to pain, kinematics, and kinetics of the lower limb joints in addition to mechanical and energetic variables.

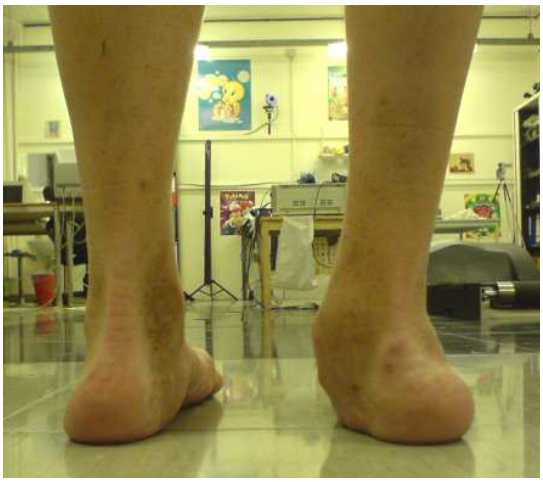

Fig. 14. Severe arthropathy of the right ankle showing a characteristic planovalgus deformation

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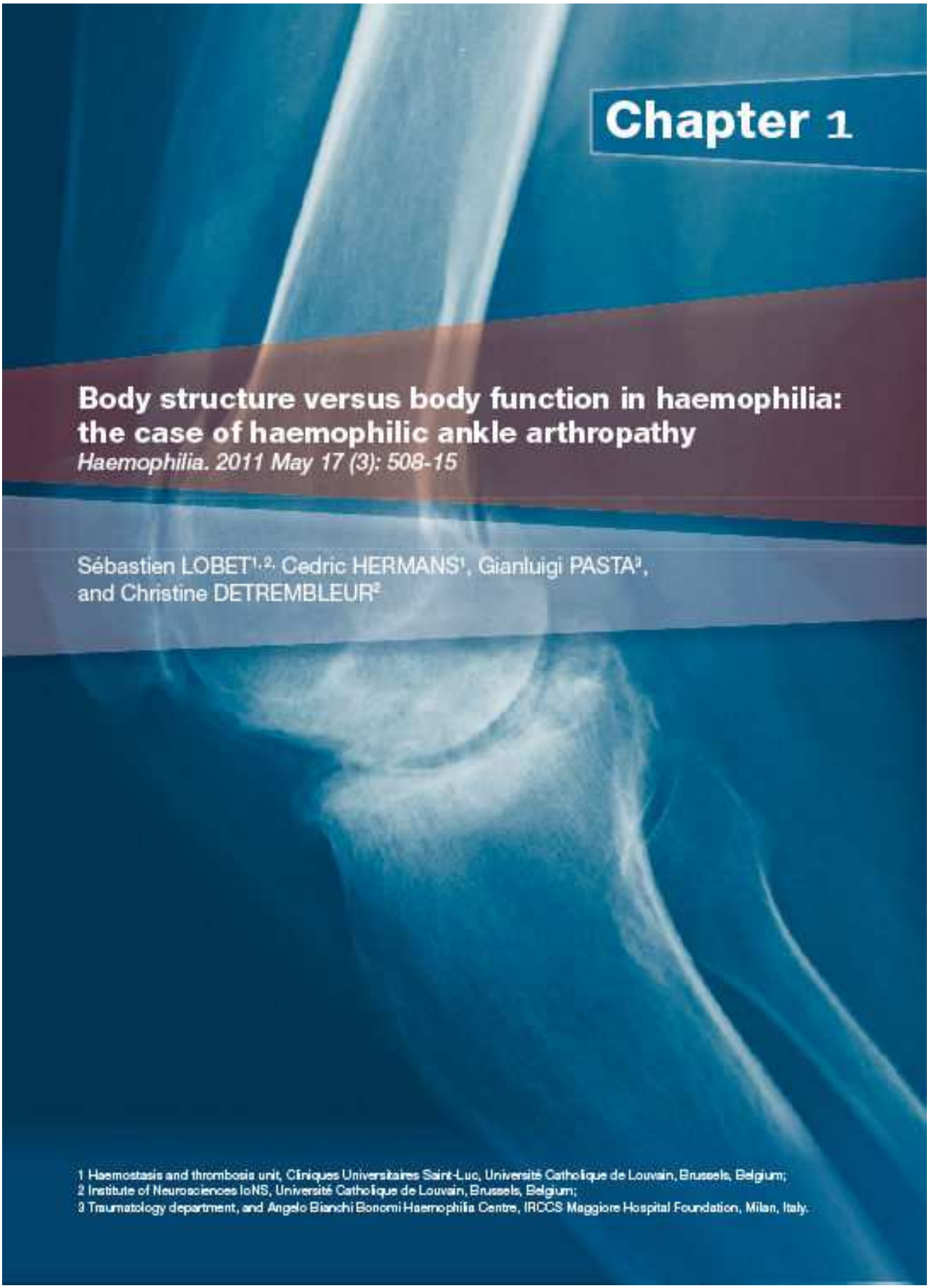
Section 1

Pathophysiology of gait in patients with haemophilia



Chapter 1

Body structure versus body function in haemophilia: the case of haemophilic ankle arthropathy

Haemophilia. 2011 May 17 (3): 508-15

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Summary

Imaging and clinical scores are the main tools used to evaluate the progression of haemophilic arthropathy (HA). Based on haemophilic ankle arthropathy, this study aimed to explore the concordances between structural and clinical alterations, determined by standard radiological and clinical scores, and functional alterations assessed by three-dimensional gait analysis (3DGA). In total, 21 adult haemophilia patients underwent extensive ankle evaluation using the physical examination part of the World Federation of Haemophilia joint score, the Arnold–Hilgartner and the Pettersson radiological scores, and self-reported ankle function assessment using the revised Foot Function Index. Significant associations were found between self-reported ankle function assessment and the three 3DGA variables representative of joint function (range of motion, peak plantar flexion moment, and peak power generated at the push-off phase). Radiological and clinical scores were compared with ankle muscle peak power measurement, the most reliable 3DGA gait variable for ankle function. No significant associations were found between both clinical and functional scores and the 3DGA functional assessment. This discordance may be explained by the lack of a direct relationship between functional alterations detected by 3DGA and the structural changes assessed using X-ray or clinical scoring. Another explanation may be the limitation of clinical and radiological scoring systems in properly determining the severity of HA. Functional assessments such as 3DGA should be used more frequently when monitoring the progression of ankle arthropathy or the effects of therapeutic interventions in adult haemophilia patients.

Introduction

Recurrent bleeding episodes in joints (haemarthroses) and muscles (haematoma) are major complications of haemophilia. Long-term consequences of repeated haemarthrosis include joint cartilage damage and irreversible chronic arthropathy resulting in severe impairments, activity limitation and participation restriction.

As recommended by the World Health Organization, joint assessment in haemophilia patients should be performed according to the International Classification of Functioning, Disability and Health (ICF) [1]. Published in 2001, this conceptual model provides a framework for clinical practice, teaching, and research, representing the reference for existing health-related measures. The ICF model is composed of 'body structures and functions', 'activities', and 'participation' domains (Fig. 1).

As regards to haemophilia, the 'body function and structure' domain has traditionally been evaluated using both radiological and clinical joint scoring scales. These scores have been used in clinical practice to evaluate the effects of therapeutic interventions, such as clotting factor prophylaxis, physical therapy, and surgical procedures, on arthropathy progression [2]. While radiological scores only provide information about the anatomical joint structure ('body structure' component), clinical joint assessment integrates both 'body function' and 'body structure' components.

The direct relationship between 'body functions' and 'body structures' is still being debated. In patients presenting knee osteoarthritis, some authors have reported a poor correlation between certain joint function parameters and structural changes detected using X-rays [3,4]. Similarly, Rodriguez-Merchan [5] reported that haemophilic arthropathy (HA) joints may retain appropriate function over several years, despite severe radiographic destruction.

Given the importance of radiological and clinical scores in the routine assessment of HA, the 'body function and structure' domain must be clarified. As the ankle has become the most frequently affected joint in haemophilia patients [6], our centre's priority is to focus on clinical research in ankle HA. Using the ankle joint as an example, our study aimed to explore the relationship between clinical and radiological scores, *i.e.,* the 'body structure' domain and the 'body function' domain based on three-dimensional gait analysis (3DGA) lower limb assessment. Contrary to radiological and clinical scores, 3DGA allows for an objective quantification of joint motion, muscle moment, and power under dynamic and weight-bearing conditions. As this approach generates extensive data, we first identified which of the 3DGA variables was the most relevant for joint function in adult haemophiliacs.

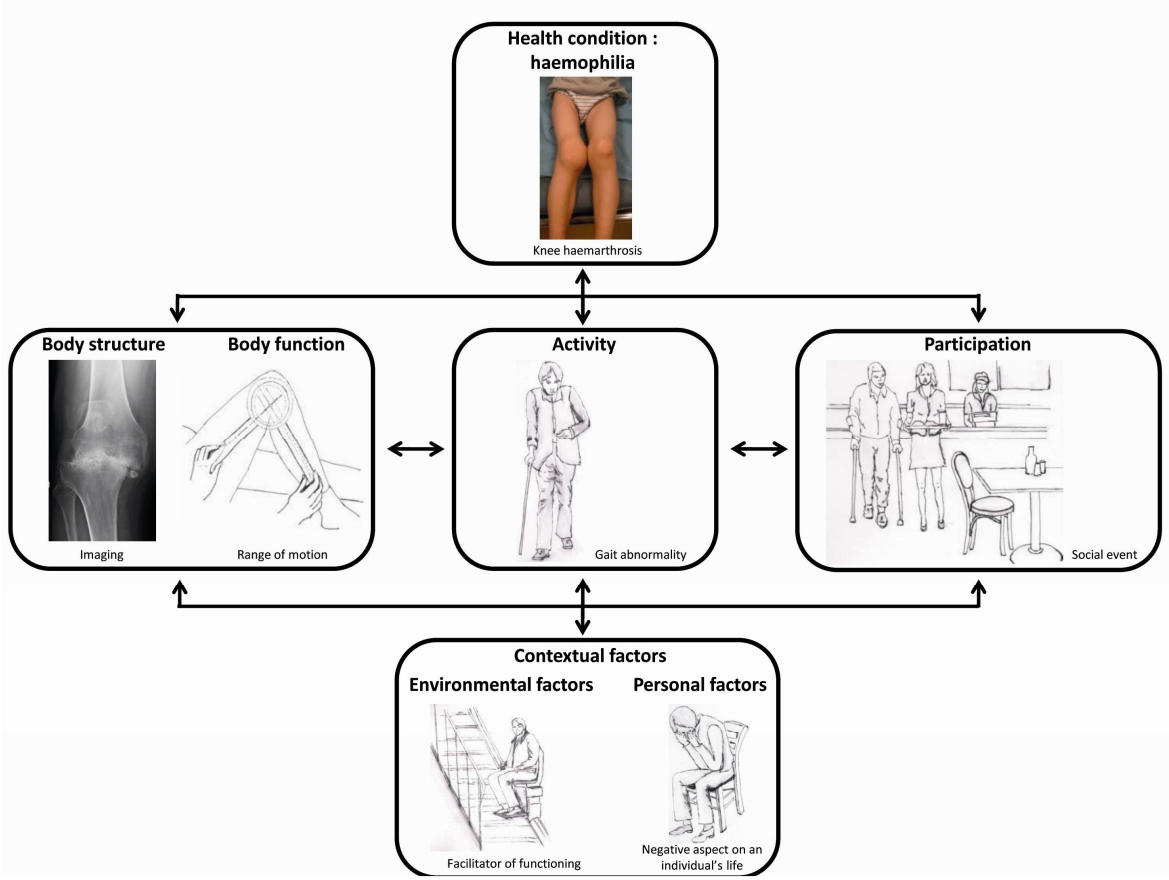

Fig. 1. Disability assessment according to the ICF model. The major complications experienced by haemophilia patients (the 'health disorder') are recurrent episodes of bleeding in the musculoskeletal system, which may lead to changes in 'functioning and disability' components, composed of 'body structures and functions', 'activities', and 'participation' domains. 'Body structures' are body parts, such as organs, limbs, and their components. 'Body functions' are defined as the physiological functions of these systems, such as range of motion, strength, and stability. In haemophilia patients, the 'body function and structure' domain is currently assessed using clinical and radiological scores [7,9,10]. X-ray, ultrasonography, and MRI assessments are by definition strictly focused on the 'body structure' aspect of impairment. The clinical scores such as the WFH score and the Haemophilia Joint Health Score (HJHS) [34] integrate both impairment aspects of 'body function' and 'body structure'. Currently, 3DGA is designed to focus on functional assessment. 'Activities' involve executing tasks or actions that can be performed by the individual. Activity limitations (*e.g.* the inability to climb or go down stairs and the difficulty to shave due to elbow arthropathy) can be measured using two haemophilia-specific scores: a self-report score, the Hemophilia Activities List (HAL) [35], and a performance-based score, the Functional Independence Score for Haemophilia (FISH) [36,37]. 'Participation' is defined as the involvement in a life situation such as sport, work, leisure, or a social event. At present, no specific suggestions have been made with regard to the evaluation of the restrictions in the 'participation' domain [38]. The components of 'functioning and disability' can be affected by 'contextual factors', which represent a person's background and include both 'environmental factors' and 'personal factors'. 'Environmental factors' consist of the physical, social and attitudinal environment in which an individual lives and conducts day-to-day activities. These factors are either barriers to, or facilitators of, functioning. They include the positive or negative attitude of family, colleagues, and neighbors, as well as the architectural barriers and technical aid that the haemophilia patient with impaired mobility confronts. 'Personal factors' include the aspects of an individual's life that are not necessarily part of the condition or health status, such as age, social background, education, profession, as well as past and current experiences.

Materials and methods

Subjects

In total, 21 haemophilia patients regularly followed up at the Haemophilia Comprehensive Centre of the Brussels *Cliniques Universitaires Saint-Luc* in Belgium were enrolled between March 2008 and November 2009. Their characteristics are presented in Table 1. All subjects had bilateral ankle HA. Assessment tool characteristics are summarized in Table 2. The study was approved by the local ethics committee, and all patients gave written informed consent.

Table 1. Characteristics of the study group (n=21)

Age (years)	39 ± 9 (21-60)
Weight (kg)	81 ± 15 (60-123)
Height (m)	1.75 ± 0.05 (1.66–1.85)
BMI (kg/m^2)	26.0 ± 4.9 (19.3-38.8)
Haemophilia A/B	(20/1)
Factor deficiency (severe/moderate/mild)	(20/1/0)
Clinical assessment	
Ankle arthropathy (unilateral/bilateral)	21 (0/21)
Knee arthropathy without surgery (unilateral/bilateral)	5 (2/3)
Total knee replacement (unilateral/bilateral)	10 (4/6)
Total hip replacement (unilateral/bilateral)	2 (2/0)
Elbow arthropathy (unilateral/bilateral)	18 (3/15)
Shoulder arthropathy (unilateral/bilateral)	3 (0/3)
Medical treatment	
Prophylaxis/on-demand treatment	(9/12)
Use of NSAID (daily/on demand/none)	(6/5/10)

Values are mean ± SD (range)

BMI: body mass index; NSAID: nonsteroidal anti-inflammatory drug; SD: standard deviation.

Clinical and radiological assessments

All subjects underwent ankle evaluation by the same investigator using the physical examination part of the World Federation of Haemophilia joint score (WFH score) [7], the most widely used clinical assessment instrument for HA [8]. Radiological evaluation of ankles was performed by a senior, highly experienced orthopaedic surgeon using the Arnold–Hilgartner (A-H) [9] and Pettersson [10] radiological scores. The A-H scale is based for the most part on the roentgenographic findings and attempts to separate the joint changes into stages that have surgical significance [9]. In contrasts, the Pettersson classification [10] is an additive system based on the presence or absence of eight specific radiographic features. The disadvantage of the A-H scale is that both early and late findings may be present but the score reflects only the late findings [8]. The two scales also differ in that the A-H scale includes soft-tissue changes whereas the Pettersson score does not grade soft-tissue

changes. For these conceptual differences and although the Pettersson score has been adopted by the WFH we decided to use both radiological scores.

Table 2. Summary of the tools used in this study in order to assess ankle joint

Structural assessment	
A-H radiological joint score	Progressive scale (the most advanced change determines the score) Based on six radiographic stages Ranges from 0 (normal joint) to 5 (end-stage arthropathy)
Pettersson radiological score	Additive system (the sum of changes determines the score) Based on the presence or absence of eight specific radiographic features Ranges from 0 (normal joint) to 13 (end-stage arthropathy)
Combined structural and fonctional assessment	
WFH clinical score	Additive system Based on seven components including both aspects of "body function" (joint ROM, flexion contracture, joint instability, crepitus with motion) and "body structure" (swelling, muscle atrophy, axial deformity) Ranges from 0 (normal joint) to 12 (end-stage arthropathy)
Functional assessment	
FFI-R short-form	Region-specific outcome instrument Additive system Global score assessing both feet together Each item assesses foot function over the past week Ranges from 0 to 30 (maximum pain score) or 36 (maximum stiffness score)
3DGA	Simultaneous analysis of joint kinematic (modeling of body segment movements) and kinetic (force interactions of the foot with the ground) Allows to objectively quantify joint motion, muscular moment and power in a dynamic and weight-bearing condition Good reproducibility, sensitivity and sensitivity to change

A-H score: Arnold-Hilgartner score; WFH: World Federation of Hemophilia; ROM: range of motion; FFI-R: Foot Function Index-Revised short-form; 3DGA: three-dimensional gait analysis

Foot-specific functional assessment

Given its psychometric properties, wide applicability, and capacity to reliably assess foot problems, the Foot Function Index-Revised short-form (FFI-R) [11] was selected using the following subscales: pain, stiffness, disability, limitation in activity and social/emotional issues. Each item in the FFI-R assesses foot function over the past week. The ‘pain’ and ‘stiffness’ subscales are clearly defined in the ICF model as part of the ‘body function’ (ICF-B28016 and B780 respectively). The ‘disability’ subscale is part of the ‘activity limitation’ in the ICF-model, whereas the ‘activity limitation’ subscale is misused and refers more to the ICF-‘participation restriction’ in the same way as the ‘psychosocial issues’ subscale. The

'pain' and 'stiffness' subscales, clearly defined in the ICF model as part of the 'body functions', were therefore the only subscales retained for functional joint assessment.

Gait analysis

The technical aspects of 3DGA in haemophilia patients have been published previously [12]. All 3DGA assessments were performed by the same investigator. At analysis, patients had been free of acute joint or muscle bleeding for the previous 30 days. While the patient was walking on a treadmill with neutral running shoes (Kalenji success Decathlon®, Villeneuve d'Ascq, France), a system composed of six infrared cameras (Elite system V5; BTS, Garbagnate Milanese, Italy) recorded the trajectories of reflective markers positioned on specific anatomical landmarks on the patient's skin, close to the joint centres or fixed to limb segments (joint kinematics). Joint angle data provide information on the relative segment positions during the gait cycle, making it possible to measure the active range of motion (AROM) (Fig. 2a). A force platform composed of four 3D strain-gauge force transducers located under the treadmill simultaneously measured the ground reaction forces generated by the body in three directions: vertical, lateral and forward [13]. The net moments of force and power generated or absorbed at the major joint muscles of the ankle in the sagittal plane were estimated [14].

Joint moments categorize the type of movement generated by dominant muscles, *i.e.,* plantar or dorsiflexion moment, and are the product of the ground reaction force generated by the lever arm. The magnitude and timing of moments were evaluated (Fig. 2b). Joint power is related to the muscle contraction type. A net positive power is typically associated with concentric muscle contraction, whereas a net negative power is linked to eccentric muscle contraction (Fig. 2c). Joint power was calculated as the product of the ankle angular velocity and the net joint moment. Angular velocity is the time derivative of angular displacement, which means that joint power is indirectly influenced by joint range of motion (ROM). For instance, limited ankle plantar flexion at the push-off phase (Fig. 2a) leads to reduced angular velocity in the ankle joint, and thus decreased ankle power (Fig. 2c). Joint moments and ground reaction forces (rather than joint kinematics) are more descriptive of antalgic gait in canines and humans [15,16]. For instance, joint moment is sensitive to pain-induced modifications in a single leg support. Kinematic and kinetic variables were simultaneously recorded for both legs (n=42) for 20s and averaged for 10 successive strides. The mean of each value was used for statistical analysis.

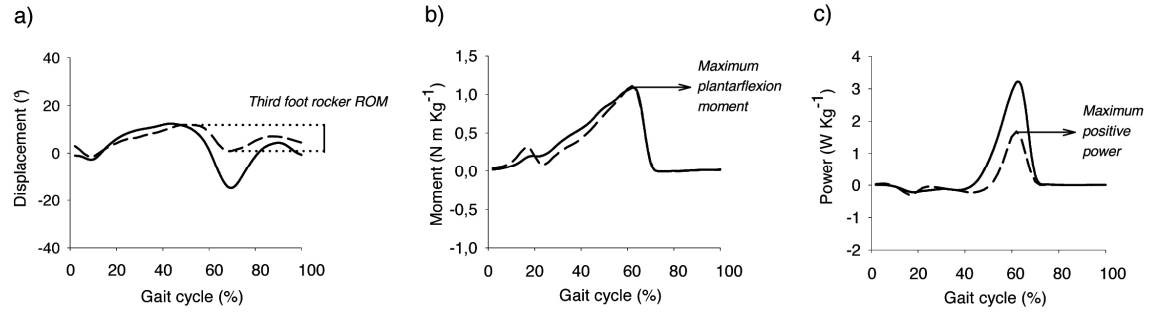

Fig. 2. Typical tracings of sagittal plane ankle kinematics (a), moment (b), and power (c) for a normal subject (solid line) and a patient with severe haemophilic arthropathy (dotted line) Variables are expressed as a function of the normalised gait cycle (%). (a) The angular displacement (°) is presented: 0°, positive and negative values indicate neutral position, dorsiflexion, and plantar flexion positions of the ankle, respectively. The magnitude between the dotted lines represents the ankle active ROM (AROM), useful for the forward propulsion of the body at each step (third foot rocker). Third rocker occurs when the plantar flexor muscles move the ankle from dorsiflexion into plantar flexion during push-off at the end of the stance phase. This AROM is generally decreased in severe ankle arhropathy cases. (b) The major moment (N m kg^{-1}) in the ankle is essentially a plantar flexion moment conducted by the calf muscles. (c) The power generated by the ankle muscles (W kg^{-1}) is essentially positive and represents the concentric contraction of the calf muscle at the end of the stance phase in order to elevate the body. In severe ankle arthropathy cases, this power is often decreased.

Statistics

The association between the 3DGA variables, ankle-specific function (FFI-R pain and FFI-R stiffness), and clinical and radiological scores was examined using a Spearman rank correlation (sigma stat v2.0 for Windows; Systat Software Inc®, Chicago, IL, USA). Of note is that subjects walked at a self-selected speed (1.10±0.18 m s^{-1}), whereas all 3DGA variables are speed-dependent [17], and kinematic and kinetic amplitudes linearly increase with increased walking speed. To limit the influence of speed, we also compared the FFI-R and the clinical and radiological scores with speed-standardized gait variables by transforming the ankle AROM, moment, and power into Z-score [18]. The Z-score is a dimensionless quantity derived by subtracting the healthy control population mean from an individual raw score and then dividing the difference by the healthy control population standard deviation: $Z\text{-score}=(X-\mu)/\sigma$ where X is the raw score of the patient, μ the mean of the healthy control population walking at the same speed as the patient, and σ the standard deviation of this healthy control population. Finally, the Z-scores were transformed into percentile to obtain a linear scale.

Results

Most relevant 3DGA variables for ankle function

Ankle results using clinical, radiological and functional tools are summarized in Table 3. A significant association was found between self-reported ankle function assessment, measured by the FFI-R (pain and stiffness subscales), and the three 3DGA variables representative of joint function (AROM used for the forward propulsion of the body at each step, peak plantar flexion moment and peak power generated at the push-off phase) (Table 4). The strongest association was observed between self-reported pain/stiffness assessment and ankle power. In fact, there was a negative correlation coefficient between ankle pain and ankle power (r_s=-0.64; P=0.002), and between ankle stiffness and ankle power (r_s=-0.75; P<0.001). Ankle power was thus selected as the most representative 3DGA variable of ankle function. When normalized by the walking speed, the ankle moment and power were the only 3DGA variables significantly correlated with FFI-R stiffness subscale.

Of note is that within the FFI-R, the pain and stiffness function subscales exhibited an excellent correlation of 0.88 (P<0.001), indicating an overall agreement with the functional impact of ankle HA.

Table 3. Results of ankle assessment

Ankle clinical assessment [n=42 (21 x 2 for both legs)]	
WFH score	5 ± 2 (1-10)
Ankle radiological assessment (N=42)	
A-H score	4 [4;4]
Pettersson score	8 [7;9]
Ankle FFI-R assessment (N=21)	
Pain subscale (max.=30 pts)	11 ± 4 (5-19)
Stiffness subscale (max.=36 pts)	15 ± 5 (6-28)
Ankle 3DGA assessment (N=42)	
AROM (°)	14.4 ± 3.9 (8.4-24.2)
Speed-normalized AROM (percentile)	0.3 [0.04;1.2]
Peak muscular moment ($N.m.kg^{-1}$)	1.02 ± 0.28 (0.44-1.62)
Speed-normalized peak muscular moment (percentile)	50.4 ± 28.6 (7.0-95.8)
Peak muscular power ($W.kg^{-1}$)	1.89 ± 0.94 (0.63-4.03)
Speed-normalized peak muscular power (percentile)	9.2 [3.9;30.7]

Values are mean ± SD (range) or median [P25;P75]

WFH, World Federation of Hemophilia; A-H score, Arnold-Hilgartner score; FFI-R, Foot Function Index-Revised short-form; 3DGA, three-dimensional gait analysis; AROM, active range of motion; SD, standard deviation.

Table 4. Correlations between FFI-R functional subscales, clinical/radiological scores and 3DGA variables (n=21)

	WFH clinical score[a]	A-H radiological score[a]	Pettersson radiological score[a]	3DGA AROM[a]	Speed-normalized 3DGA AROM[a]	3DGA Moment[a]	Speed-normalized 3DGA Moment[a]	3DGA Power[a]	Speed-normalized 3DGA Power[a]
FFI-R pain	0.28[b]	0.16	0.13	-0.50*	0.19	-0.59*	-0.43	-0.64**	-0.32
	0.23[c]	0.50	0.59	0.03	0.42	0.006	0.06	0.002	0.17
FFI-R stiffness	0.38	0.34	0.37	-0.65**	-0.03	-0.64**	-0.48*	-0.75**	-0.50*
	0.10	0.14	0.11	0.002	0.90	0.003	0.03	<0.001	0.02

[a] Summed value for both ankles

[b] Spearman correlation coefficient

[c] *P-value* *P<0.05; **P<0.005

FFI-R: Foot Function Index-Revised short-form; 3DGA: three-dimensional gait analysis; WFH: World Federation of Hemophilia; A-H radiological score: Arnold-Hilgartner radiological score; AROM: active range of motion.

Relationship between ankle function and clinical/ radiological findings

In contrast, no correlation was found between both the clinical and radiological scores and the ankle function, as measured by the 3DGA ankle power indicator. The correlation coefficients were -0.27 (P=0.08), -0.25 (P=0.11), and -0.24 (P=0.12) for the clinical WFH score, A-H radiological score, and Pettersson radiological score respectively (Table 5). Similarly, no correlation was observed when the ankle power was normalized by the walking speed to eliminate the effect of speed.

No significant correlation was found between the cumulated radiological/clinical scores for both ankles and the FFI-R pain and stiffness subscales (Table 4).

As expected, a strong Spearman rank correlation was observed between the radiological A-H and Pettersson scores (r_s=0.84; P<0.001), indicating an overall between-rater agreement as regards the radiological severity of the HA. There were moderate but significant correlations between the radiological scores and the clinical assessment, the correlation coefficients between the radiological A-H and Pettersson scores, and the clinical WFH score being 0.60 (P<0.001) and 0.59 (P<0.001) respectively.

Table 5. Correlations between ankle power, speed-normalized ankle power, clinical and radiological scores (n=42).

	WFH clinical score	A-H radiological score	Pettersson radiological score
3DGA Ankle Power	-0.27[a]	-0.25	-0.24
	0.08[b]	0.11	0.12
3DGA Speed-normalized ankle Power	-0.26	-0.28	-0.26
	0.10	0.07	0.10
WFH clinical score		0.60**	0.59**
		<0.001	<0.001
A-H radiological score			0.84**
			<0.001

[a] Spearman correlation coefficient.

[b] *P-value* *P < 0.05; **P < 0.005.

WFH, World Federation of Hemophilia; A-H radiological score, Arnold-Hilgartner radiological score; 3DGA, three-dimensional gait analysis.

Discussion

In haemophilia care, assessing lower limb joints is of paramount importance for diagnosis of HA, treatment initiation, prevention of disease progression, and comparison of various treatment strategies [19]. According to the ICF model [1], joint impairments in haemophilia patients may stem from structural and functional abnormalities (Fig. 1), which can be evaluated radiologically or clinically with various scoring systems. Radiological examinations such as X-ray and magnetic resonance imaging (MRI) are strictly focused on the 'body structure' aspect of impairment, whereas the clinical scores such as the WFH score [7] focuses on both the 'body function' and 'body structure' aspects. In clinical practice, joint function is frequently assessed under non-weight-bearing conditions, whereas it was assessed using 3DGA in our study. The originality of this technique is to estimate accurately the active ROM, moments, and power of lower limb joints during the act of walking, *i.e.*, under weight-bearing conditions.

As confirmed in the first part of our study, ankle power is probably the most representative 3DGA variable for ankle function. A significant association was found between self-reported ankle function assessment, measured by the FFI-R and the peak power generated at the push-off phase (Table 4).

In the second part of our study, we found no correlation between radiological/clinical scores and ankle joint function evaluated by 3DGA (Table 5, Fig. 3). As previously reported, numerous authors failed to demonstrate an association between radiological features of osteoarthritis (OA) and joint function. Szebenyi *et al*. [4] reported a lack of concordance between the radiological diagnosis of knee OA, pain and global function scores. Similarly, Barker *et al*. [3] reported that OA radiological scores did not predict function. The same discordances are likely to hold true for haemophilia patients, although a few authors [8,20] reported an association between clinical/radiological scores and joint function. Several authors have raised the question whether clinical and radiological scales accurately reflect the severity of HA [5,19–24]. Rodriguez-Merchan [5] described the phenomenon where adult haemophiliac joints, with severe radiological damage, seemed to function reasonably well for many years. In 2004, Manco-Johnson *et al*. [19] reported that applying the clinical WFH score to young children on intensive prophylactic treatment regimens proved unsatisfactory, as this scale scored very limited data. Manco-Johnson also reported that children whose physical disability visibly differed in severity to the casual observer could achieve identical clinical WFH scores. In 1988, Hamel *et al*. [21] reported interesting case studies in which significant radiological changes did not always parallel changes in the clinical WFH score. To illustrate their point, the authors referred to a patient presenting avascular necrosis of the talus, collapse of the talar dome, and advanced arthritic changes (Pettersson radiological score of 6/13). Yet, this patient exhibited only minor changes at the clinical

assessment (clinical WFH score of 1/12: painful joint with moderate impairment of the ROM).

Two hypotheses can be proposed to explain the absence of a relationship between the clinical/radiological scores and joint function. The first hypothesis is based on the potential lack of a direct relationship between both aspects of the ICF-components (body function and structure). In 1992, Hadler [25] noted that, 'The epidemiology of osteoarthritis and the epidemiology of pain have little in common, not nothing in common, but surprisingly little'. Although pain represents only one aspect of joint function, the author stated that X-ray images do not always accurately reflect joint function. Interestingly, a strong correlation between the A-H and the Pettersson radiological scores (r_s=0.84; P<0.001) was observed in our study. Similarly, a strong relationship between MRI, ultrasound, and X-ray images has previously been reported for HA [26,27]. This is indicative of an overall agreement as regards the structural severity of HA but not necessarily the joint function. The only possible way to validate this hypothesis would be to compare 3DGA functional assessment with a technique that correctly depicts joint structure, such as MRI. MRI provides detailed information on arthritic changes, is sensitive enough to detect even subclinical manifestations of arthropathy, and is considered to be the gold standard for structural haemophilic joint assessment [28–30]. However, due to its high costs, it is difficult to justify MRI as a clinical research tool.

The second hypothesis is that clinical and radiological scores are not well adapted to assess adult HA objectively. Radiological scores have previously been criticized, as they underestimate the degree of joint pathology in the early stages of HA [30], and exhibit low inter- and intra-observer reliability rates in mild and moderate HA [2]. A similar lack of psychometric properties and the underestimation of the severity of arthropathy were emphasized for the clinical WFH score [27,31]. In our study population (Table 1, Fig. 3), the distribution of the A-H and Pettersson radiological scores (4/5 [4;4] and 8/13 [7;9] respectively) was not Gaussian, and most patients were classified as having severe arthropathy. This was probably a result of the radiological scoring system, which is unable to discriminate between different stages of severe OA. In HA, structural changes develop over decades. Once radiological changes are present, the structural changes are usually progressive and irreversible [30]. Improved therapy has led to the need for more sensitive tools in assessing joint damage, capable of detecting subtle joint changes. In this context, 3DGA functional assessment generates continuous variables that have been proven to be sensitive to changes resulting from natural disease progression [12] or stemming from medical treatments, such as non-steroidal anti-inflammatory drugs [32].

One limitation of our study is that it was focused on the ankle joint only. While Aznar *et al*. [33] previously reported that the ankle was the most radiologically damaged joint in haemophiliacs. However, Wallny *et al*. [20] found precisely for the ankle, the lowest correlation between joint function (pain evaluated by visual analogue scale) and the WFH

score and Pettersson radiological score. Ideally, we should conduct a similar study focused on the knee joint. We chose the ankle arthropathy for practical reasons. As the ankle has become the most frequently affected joint in haemophiliacs [6], our centre's priority is to further build up fundamental and clinical research in ankle HA.

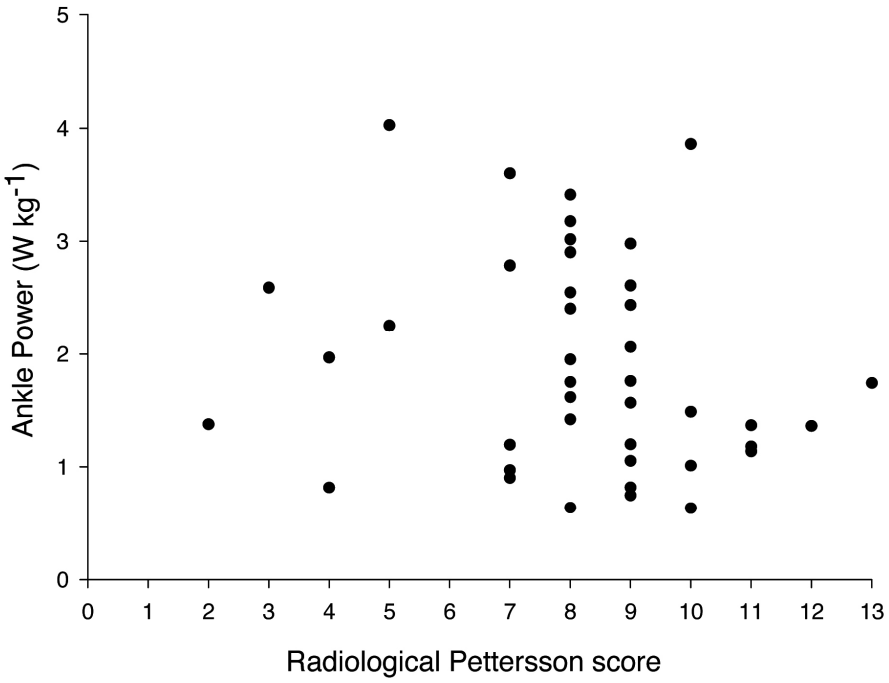

Fig. 3. Scatter plot of the relationship between ankle structure changes evaluated by the Pettersson radiological score and the ankle function represented by 3DGA ankle power. Note the relative absence of correlation between these two variables. For ankles presenting the same radiological deficit, there is a great disparity among the power generated during the propulsive gait phase.

Conclusion

This study focused on the ankle joint failed to find an association between the radiological and clinical scores traditionally used to assess adult HA and a new joint function assessment using clinical 3DGA. When monitoring blood-induced joint damage or treatment effects in haemophilia patients, clinical practitioner should be therefore aware that clinical and radiological scores do not properly integrate the joint function, but rather focus on the structural aspect of the joint.

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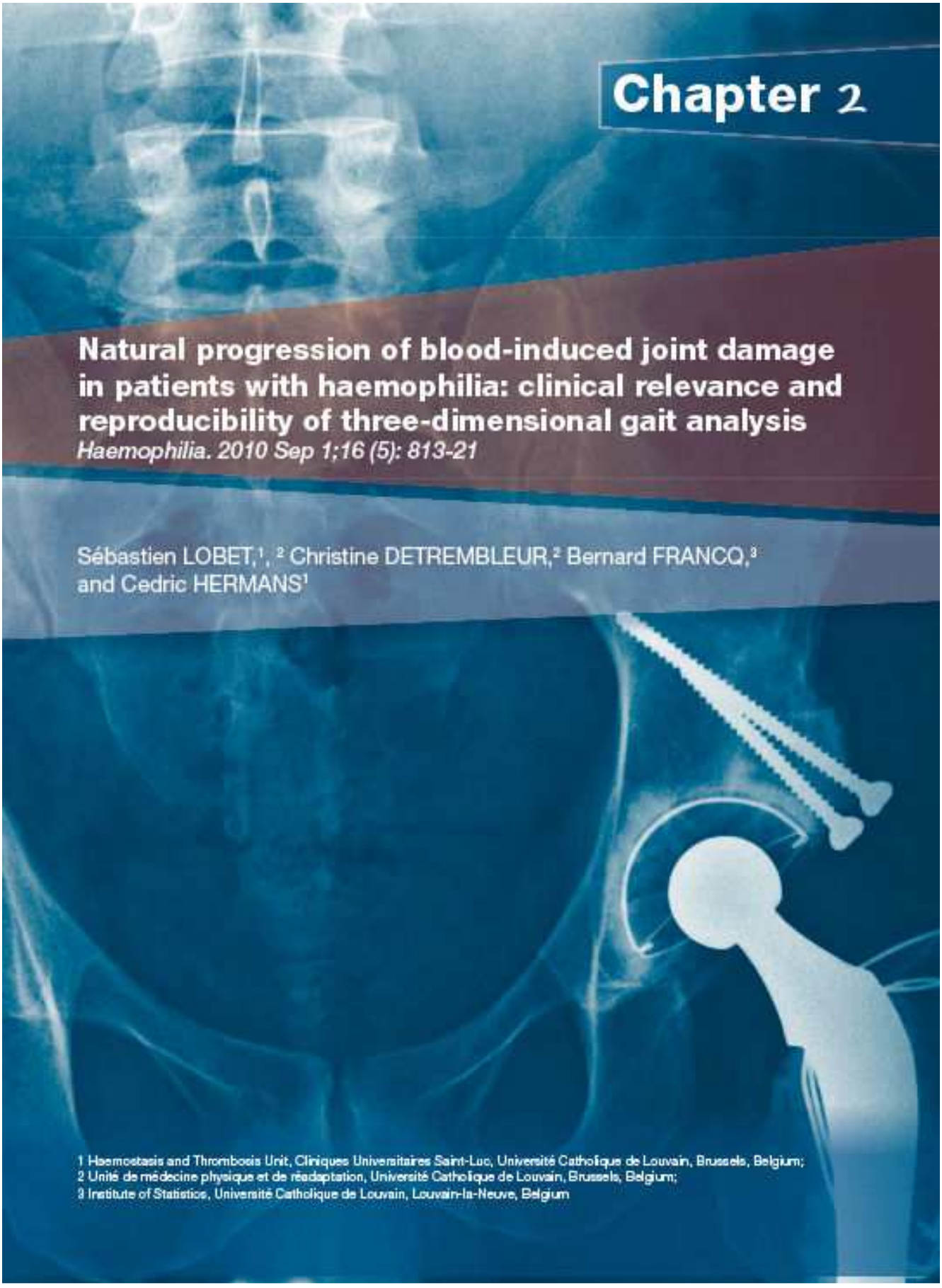

Chapter 2

Natural progression of blood-induced joint damage in patients with haemophilia: clinical relevance and reproducibility of three-dimensional gait analysis

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Summary

A major complication in haemophilia is the destruction of joint cartilage due to recurrent intra-articular and intra-muscular bleeds. Therefore, joint assessment is critical in order to quantify the extent of joint damage, which has traditionally been evaluated using both radiological and clinical joint scores. Our study aimed to evaluate the natural progression of haemophilic arthopathy using three-dimensional gait analysis (3DGA), and to assess the reproducibility of this technique. We hypothesized that the musculoskeletal function was relatively stable in patients with haemophilia. Eighteen adults with established haemophilic arthropathies were evaluated twice by 3DGA (mean follow-up: 18±5 weeks). Unexpectedly, our findings revealed infraclinical deterioration of gait pattern, characterized by a 3.2% decrease in the recovery index, which is indicative of the subject's ability to save energy while walking. A tendency towards modification of segmental joint function was also observed.Gait analysis was sufficiently reproducible with regards to spatiotemporal parameters as well as kinetic, mechanical, and energetic gait variables. The kinematic variables were reproducible in both the sagittal and frontal planes. In conclusion, 3DGA is a reproducible tool to assess abnormal gait patterns and monitor natural disease progression in haemophilic patients.

Introduction

The major complications experienced by patients with haemophilia are recurrent bleeding episodes into the musculoskeletal system, not only into the joints (haemarthrosis) but also the muscles (haematoma). Destruction of the joint cartilage and irreversible chronic arthropathy are the long-term consequences of repeated haemarthrosis, causing severe and painful functional disability, loss of autonomy, and altered quality of life. One of the major goals of medical treatment of haemophilia is to minimize joint structural damage by preventing haemarthrosis. This can be achieved by regular intravenous infusions of plasma-derived or recombinant concentrates of clotting factor VIII or IX, administered as either prophylactic therapy or on-demand therapy.

Musculoskeletal assessment is critical in order to quantify the extent of articular damage and evaluate therapeutic interventions in patients with haemophilia [1]. This has traditionally been evaluated using both radiological [2,3] and clinical joint scores [4]. Long-term musculoskeletal outcomes have been assessed using these scores, correlating with the intensity of factor replacement therapy [5]. Although the development of radiological and clinical scores signify an invaluable contribution to haemophilia care, these scores exhibit several limitations, such as a lack of psychometric properties (reliability, validity, and sensitivity to change) as well as their inability to detect early changes in the haemophilic joint [6,7]. This has prompted the development of more sensitive scoring systems based on magnetic resonance imaging (MRI) [7], as well as new clinical scores such as the Hemophilia Joint Health Score (HJHS) [8]. However, as both clinical and radiological scores are based on the status of individual joints, they do not integrate the global and inter-related impact of multiple-joint arthropathy on musculoskeletal function.

An adequate assessment of the musculoskeletal system should take into account the wide spectrum of haemophilic arthropathy, which ranges from small or absent joint damage in young children on primary prophylaxis to severe disabling arthropathy in poorly or inefficiently treated patients. Joint evaluation should be sensitive enough to detect early articular changes, in order to minimize the impact of joint destruction. In patients with established arthropathy, joint assessment should enable evaluation of the global functional status, as well as the impact of limited or diffuse arthropathy on the musculoskeletal system, in order to offer a tailored treatment.

Three-dimensional gait analysis (3DGA) is a promising approach for joint function assessment in haemophilic patients. 3DGA consists of simultaneous analysis of joint kinematic (modeling of body segment movements), kinetic (study of the force interactions of the foot with the ground), and metabolic measurements (calculation of energy consumption). Over the last few decades, 3DGA has evolved significantly due to advances in computer technology and data analysis techniques [9]. The technique allows for the objective quantification of motion, permitting the better understanding of normal and

abnormal movement gait patterns. To date, 3DGA has been widely used in the clinical decision-making process, and to predict the outcome of therapeutic interventions in various neurological or orthopedic disorders [10-17].

The purpose of this study was primarily to evaluate the reproducibility of 3DGA in adults with haemophilia by measuring kinematics, kinetics, and metabolic gait variables. Gait analysis has shown to be an important tool in determining biomechanical factors that may influence the outcomes of degenerative joint diseases such as osteoarthritis [10]. The second objective of our study was to estimate the natural progression of haemophilic arthopathy using 3DGA. We hypothesized that the musculoskeletal function in patients with haemophilia is relatively stable. For this reason, musculoskeletal function should not differ when evaluated by an intersession comparison within a short time interval.

Materials and methods

Subjects and experimental design

Eighteen patients with haemophilia regularly followed at the Haemophilia comprehensive center of the *Cliniques Universitaires Saint-Luc*, Brussels, Belgium, were enrolled in the study between March 2008 and June 2009. Their characteristics are presented in Table 1. The study was approved by the Local Ethical Committee, and all patients gave written informed consent.

Table 1. Characteristics of the study group

Variables	*n=18*
Age (years)	40 ± 10 (21-60)
Weight (kg)	81 ± 15 (60-123)
Height (m)	1.76 ± 0.06 (1.66–1.87)
Body mass index (BMI) (kg/m^2)	26.2 ± 4.8 (21–38.8)
Haemophilia A	17
Haemophilia B	1
Severe factor deficiency	16
Moderate factor deficiency	2
Clinical assessment	
Ankle arthropathy (unilateral/bilateral)	18 (2/16)
Knee arthropathy without surgery (unilateral/bilateral)	6 (3/3)
Total knee replacement (unilateral/bilateral)	8 (4/4)
Total hip replacement (unilateral/bilateral)	1 (1/0)
Elbow arthropathy (unilateral/bilateral)	13 (3/10)
Shoulder arthropathy (unilateral/bilateral)	2 (0/2)
Medical treatment (prophylaxis/on-demand)	18 (8/10)

Values are mean±SD (range) for age, weight, height and BMI.

Three-dimensional gait analysis was tested by comparing gait variables during two sessions performed by the same investigator (S.L.): at baseline (T0) and after a mean follow-up of 18±5 weeks (range: 13-33) (T1). At the time of evaluation, patients had been free of acute joint or muscle bleeding for the last 30 days. Specific attention was given to the use of non-steroidal anti-inflammatory drug (NSAID) prior to 3DGA. Subjects occasionally using NSAID were instructed to observe a wash-out period of at least 72h prior to testing, whereas those using NSAID daily were told not to interrupt the treatment. Participants were also asked to continue their replacement therapy with clotting factors before and between the 3DGA sessions.

Gait analysis

Gait was assessed using 3DGA which included synchronous kinematic, kinetic, mechanic and metabolic measurements. As this approach generates an extensive amount of variables, data interpretation and understanding may be difficult for a clinician unfamiliar with gait analysis. In an attempt to provide an overview of 3DGA in haemophiliac patients, the basic principles are summarized hereafter. Those interested can refer to technical methodological aspects in the reference list.

A major advantage of 3DGA is its ability to estimate accurately the “active” joint range of movement (ROM) in a “real” weight-bearing condition (kinematic variables) and to provide significant information on the spatial and temporal coordination between lower-limb segments (spatiotemporal parameters). In multiple and severe joint affections such as haemophilia, 3DGA may be used to pinpoint which specific joints or muscles are responsible for the functional deficit.

The sessions began with a rest period, during which the subjects stood on a motor-driven treadmill for static calibration of kinematic and energetic variables. Thereafter, the subjects were asked to walk with neutral running shoes (Kalenji success, decathlon®) for a few minutes until a steady state was reached and maintained for at least 2 minutes, in order to compute energetic variables. Other variables were simultaneously recorded for 20s and averaged for 10 successive strides. The mean of each value was used for statistical analysis. Mechanical work and energetic variables were calculated for each subject (n=18) whereas spatiotemporal parameters, kinematics and kinetics were calculated for both legs (n=36). The subjects walked at a self-selected speed at T0 (1.08±0.19 m s^{-1}). The same speed was imposed at T1 for each subject.

Segmental kinematics were measured using the Elite system (BTS, Italy). Six infrared cameras measured the 3D coordinates of reflective markers placed on specific anatomical landmarks (Fig. 1) allowing computation of the angular displacement [11,18]. Spatiotemporal

parameters were assessed thanks to the 3D position data (cadence, step length, and percentage of stance/swing phase duration). Four 3D strain-gauge force transducers located under the treadmill recorded the ground reaction forces generated by the body in 3D [19]. Kinematic and kinetic variables provide important information on the type of movement produced using the calculation of joint moment, whereas joint power allows for a better understanding of the muscles' role in producing and controlling motion [9]. The joint moment and power of the hip, knee and ankle were calculated [11,18,20]. Kinematic and kinetic data were normalized to 100%, 0% corresponding to the initial contact of the foot with the ground.

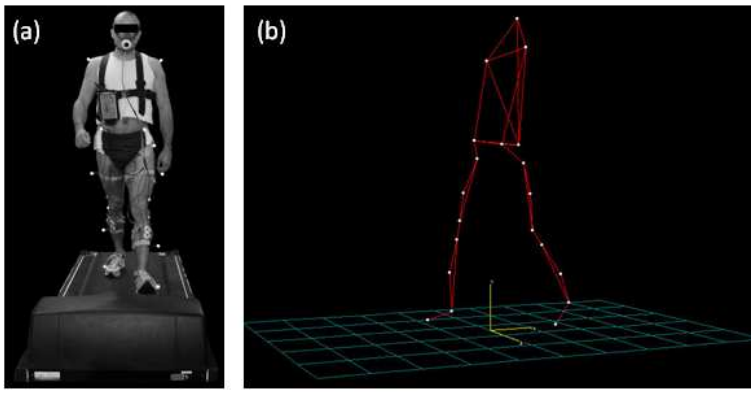

Fig. 1. Three-dimensional gait analysis. (a) The subjects walked with neutral running shoes on a custom-built motorized treadmill mounted on four 3D strain-gauge force transducers.(b) Infra-red light sources around each camera reflected the retro-reflective markers and generated reconstructed 3D trajectories. The cameras were positioned so that each marker would be seen by two cameras at any given time.

As suggested by Beeton *et al.* [1], assessment of lower extremity function is highly relevant in haemophilia care. The traditional clinical and radiological scores tend to document disease consequences at a single joint level, without reflecting the impact on the musculoskeletal function as a whole [5]. Our gait laboratory specifically aims to evaluate the repercussions of segmental abnormalities on global function by calculating more "global" indexes, such as mechanical work, cost, recovery, and efficiency. These indexes are likely to be more relevant in the objective assessment of patient problems in performing fundamental tasks such as walking. The total mechanical work (W_{tot}) done by the muscles was divided into the external work (W_{ext}) performed to move the center of body mass (CoM) relative to the surroundings, and the internal work (W_{int}) performed to move the body segments relative to the CoM [21,22]. The 'recovery' was also calculated. This index is indicative of the efficacy of the gait mechanisms, and defines the subject's ability to save energy by passively recovering kinetic energy into gravitational potential energy and back again while walking, as does an inverted pendulum [11,23].

The net metabolic cost (C_{net}) was calculated as the net oxygen consumption over the walking speed [36]. The efficiency represents the percentage of metabolic cost actually

transformed into mechanical energy by muscles, and was calculated as the ratio of W_{tot} to C_{net} [10,14,21].

Statistical analysis

Inter-session reproducibility. To be clinically meaningful, 3DGA assessment must be reproducible. Reproducibility may be defined as agreement (absolute reliability) and reliability (relative reliability) [25].

Agreement study: Agreement refers to the measurement error and assesses how close the scores are from repeated measurements. In our study, the major potential source of systematic variance was induced by a modification of the subjects' gait pattern due to the natural progression of joint disease. On the other hand, unsystematic variance consists of natural fluctuation of subjects' gait pattern as well as potential unreproducibility of the 3DGA itself. The standard error of measurement (SEM) is an agreement measure that provides an estimate of unsystematic variance [26]. As a measure of within-patient variability, it expresses the measurement error in the same units as those of the original measurement.SEM is estimated by taking the square root of the residual variance calculated by an analysis of variance for repeated measures (SIGMA STAT v2.0 for Windows) [12]. It is thus important to note that SEM is independent of the between-subject variability of the variable in the population sample [27]. The coefficient of variation of SEM (SEM%) was also calculated by dividing SEM by the mean of the measurements at T0 and T1, and multiplying by 100. Lower SEM% values reflect lower measurement errors in comparison to higher SEM% values.

The clinician may question how to interpret change score values. Is this change score beyond measurement error that would typically occur during routine 3DGA administration? The minimal detectable change (MDC), represents the safest threshold for identifying statistically detectable individual changes [28]. MDC_{95} was calculated by multiplying SEM by 1.96 and $\sqrt{2}$, where 1.96 is the two-sided tabled Z-value for the 95% confidence interval and $\sqrt{2}$ is used to account for the variance of two measurements. MDC was expressed as a percentage (MDC%) based on the same principle as SEM%. Lower MDC% values reflect greater responsiveness in comparison to higher MDC% values.

Reliability Study. Reliability reflects the extent to which a measurement instrument differentiates subjects from each other despite the measurement error. The inter-session reliability of 3DGA variables was evaluated by a two-way mixed model absolute agreement intra-class correlation coefficient (ICC) (SPSS v16.0 for windows, SPSS Inc., Chicago, IL, USA) according to Shrout and Fleiss in which an ICC≥0.75 indicates excellent reliability, between 0.75-0.40 fair to good reliability, and <0.40 poor reliability [29].

Inter-session comparison. In order to evaluate the natural progression of gait over time, comparison of 3DGA variables across the two time intervals was performed using a paired *t*-test with a Bonferroni correction (Sigma Stat v2.0 for Windows). For non-Gaussian continuous variables, Wilcoxon's signed-rank non-parametric test for paired variables was used. A *P*-value of 0.05 or less was considered statistically significant.

Results

Inter-session reproducibility

The agreement and reliability of the study results are presented in Table 2.Spatiotemporal variables showed the least measurement error, with SEM% inferior to 3%, and excellent reliability (ICC values between 0.84 and 0.96). The reproducibility of kinematics ranged from poor to excellent. In general, kinematic ROM variables were highly reproducible for the ankle, knee, and hip in both the sagittal and frontal planes. The SEM% were inferior to 13%, and ICC values were comprised between 0.79 and 0.94, except for the ankle maximum dorsiflexion at loading response (SEM%=17%, ICC=0.72). Kinematic variables in transverse plane for all the lower limb joints were least reproducible. Pelvic kinematics exhibited generally poor reproducibility, except for the frontal plane which showed moderate agreement and reliability (SEM%=19%, ICC=0.65). The reproducibility of joint position in sagittal plane at heel strike was poor for the ankle and knee, and moderate for the hip. With regard to kinetic variables, agreement at the ankle and knee levels was generally satisfactory, with SEM% comprised between 12% and 16%, except for the hip maximum flexion moment at early swing phase and the hip maximum positive power of extensor at early loading response, which showed SEM% superior to 20%.The reproducibility of mechanical and energetic variables was good to excellent, with SEM% inferior to 11% and ICC ranging from 0.80 for W_{ext} up to 0.92 for the cost. The recovery index was most likely the most stable mechanical variable, with a SEM% of approximately 3%, and an ICC of 0.90.

Calculation of the MDC_{95} and MDC_{95}% provides a frame of reference for judging change for a single 3DGA variable. For example, the MDC value for the W_{tot} indicates that for a same patient evaluated twice, a change of 0.07J kg^{-1} m^{-1} is likely to reflect a true change. Spatiotemporal parameters had the lowest MDC% values, indicating that compared to baseline, a change of 2% in stance phase duration and 8% in step length and cadence can be considered significant changes. Mechanical and energetic variables showed MDC% comprised between 10% and 30%. Kinematic ROM in sagittal and frontal planes had acceptable responsiveness, with MDC_{95}% comprised between 14% and 34%. On the contrary, the other kinematic variables were not sensitive to change, with MDC_{95}% superior to 40%. As some variables were not normally distributed, their MDC_{95} and MDC_{95}% were not meaningful.

Intersession comparison

The spatiotemporal variables changed in a very discrete manner as the mean stance phase duration adopted by patients increased from 65.2±1.5% of gait cycle at T0 to 65.6±1.5% at T1 (*P*=0.002). A small and almost significant increase of step cadence was observed (106.2±7.3 step min^{-1} *vs.* 107.5±8.0 step min^{-1}, *P*=0.058). Contrary to ankle ROM, the knee and the hip increased their movement magnitude in the sagittal plane. The knee ROM during the swing phase increased from 55.1±10.7° at T0 to 58.0±11.9° at T1 (*P*<0.001), while the hip increased from 42.1±6.1° to 43.3±5.8° (*P*=0.076). A trend towards change in joint power variables was also noted with time. A decrease in maximum ankle power at push-off phase (median value 1.93 W kg^{-1} at T0 *vs.* 1.75 W kg^{-1} at T1, *P*=0.073), an increase in knee eccentric power at swing phase (median value -1.17 W kg^{-1} at T0 *vs.* -1.28 W kg^{-1} at T1, *P*=0.075), and an increase in hip positive power at early loading response (0.47±0.23 W kg^{-1} at T0 *vs.* 0.52±0.20 W kg^{-1} at T1, *P*=0.092) were observed. A slight decrease in hip maximum flexion moment at early swing was also observed (-0.25±0.09 N m kg^{-1} at T0 *vs.* -0.22±0.10 N m kg^{-1} at T1, *P*=0.023).

With regard to the mechanical and energetic variables, a single but important change observed was related to the recovery index. An unexpected deterioration of the pendulum-like mechanism of gait was defined by a 2.1% decrease in the recovery index (65.4±8.0% at T0 *vs.* 63.3±7.9% at T1, *P*=0.01), reflecting a 3.2% impairment in regard to the baseline value at T0.

Table 2. Reproducibility study of the three-dimensional gait analysis (3DGA) variables and paired comparison between the two periods T0 and T1

	Agreement				Reliability	Paired comparison		
	SEM	SEM%	MDC_{95}	MDC_{95}%	ICC	T0[b]	T1[b]	P-value
Spatiotemporal parameters (N=36)								
cadence (step/min)	2,59	2,8	8,3	7,8	0,84	106.2 ± 7.3	107.5 ± 8.0	0,058
step length (meter)	0.02	2.9	0.05	8.0	0.96	0.68 ± 0.10	0.69 ± 0.10	0.837
stance phase duration (% gait cycle)	0.48	0.7	1.3	2.0	0.87	65.2 ± 1.5	65.6 ± 1.5	0.002**
Kinematic[a] (n=36)								
ankle dorsiflexion at heel strike (°)	2,71	32,9	7,5	91,2	0,66	8.7 ± 4.8	7.8 ± 4.5	0,157
ankle maximum flexion at loading response (°)	1,70	17,0	4.7°	47.0°	0,72	9.2 [7.3;12.6]	9.7 [7.2;12.1]	0,35
ankle sagittal ROM at push-off phase (°)	1,24	8,2	3,4	22,7	0,94	15.1 ± 4.9	15.3 ± 4.8	0,71
ankle transversal ROM (°)	1,92	23,2	5,3	64,2	0,71	8.3 ± 3.6	8.3 ± 3.5	0,934
ankle average transversal position (°)	3,24	17,7	9,0	48,9	0,74	-17.9 ± 6.8	-18.8 ± 6.0	0,22
knee flexion at heel strike (°)	4,43	53,9	12,3	149,3	0,74	7.3 ± 8.7	9.1 ± 8.9	0,087
knee maximum flexion at loading response (°)	1,95	18,1	5.4°	50.2°	0,91	12.0 [7.0;15.9]	12.2 [4.2;16.8]	0,229
knee ROM in swing phase (°)	2,92	5,2	8,1	14,3	0,91	55.1 ± 10.7	53.0 ± 11.9	<0.001**
hip flexion at heel strike (°)	4,89	15,5	13,6	43,0	0,74	32.0 ± 9.5	31.2 ± 9.8	0,597
hip sagittal ROM (°)	2,66	6,2	7,4	17,2	0,79	42.1 ± 6.1	43.3 ± 5.8	0,076
hip frontal ROM (°)	1,33	12,3	3,7	34,2	0,82	10.9 ± 3.1	10.7 ± 3.1	0,431
hip transversal ROM (°)	3,10	19,7	8,6	54,6	0,59	16.3 ± 4.8	15.2 ± 4.9	0,14
pelvic sagittal ROM (°)	1,91	57,9	5.3°	160.6°	0,02	2.9 [2.5;3.5]	2.8 [2.6;3.3]	0,677
pelvic frontal ROM (°)	1,37	19,1	3,8	52,9	0,66	7.1 ± 2.1	6.9 ± 2.2	0,172
pelvic transversal ROM (°)	2,79	43,7	7.7°	121.1°	0,47	5.1 [4.1;7.3]	5.5 [4.5;8.3]	0,677
Kinetic (n=36)								
ankle max plantarflexion moment at push-off phase (N m kg^{-1})	0,14	13,6	0,39	37,7	0,70	1.07 ± 0.22	1.02 ± 0.30	0,149
knee max extension moment at loading response (N m kg^{-1})	0,06	12,3	0,18	34,2	0,72	0.53 ± 0.12	0.53 ± 0.12	0,842
hip max extension moment at early loading response (N m kg^{-1})	0,06	12,1	0,16	33,4	0,82	0.47 ± 0.14	0.47 ± 0.12	0,902
hip max flexion moment at early swing phase (N m kg^{-1})	0,06	24,0	0,16	66,5	0,64	-0.25 ± 0.09	-0.22 ± 0.10	0.023*
ankle max power at push-off phase (W kg^{-1})	0,30	15,6	0.84°	43.3°	0,88	1.93 [1.28;2.47]	1.75 [1.14;2.74]	0,073
knee max eccentric power at swing phase (W kg^{-1})	0,19	15,1	0.53°	41.7°	0,79	-1.17 [-1.50;-0.91]	-1.28 [-1.51;-0.96]	0,075
hip max positive power of extensors at early loading response (W kg^{-1})	0,11	21,4	0,29	59,2	0,74	0.47 ± 0.23	0.52 ± 0.20	0,092
hip max positive power of flexors at early swing phase (W kg^{-1})	0,02	7,6	0,04	21,0	0,67	0.22 ± 0.10	0.20 ± 0.10	0,129
Mechanical work / Energetics (n=18)								
External work (J kg^{-1} m^{-1})	0,02	7,2	0,05	20,0	0,80	0.24 ± 0.04	0.25 ± 0.04	0,185
Internal work (J kg^{-1} m^{-1})	0,02	9,4	0,06	26,2	0,81	0.24 ± 0.05	0.24 ± 0.06	0,686
Total work (J kg^{-1} m^{-1})	0,02	5,0	0,07	13,9	0,84	0.48 ± 0.06	0.50 ± 0.07	0,184
Recovery (%)	2,19	3,4	6,1	9,4	0,90	65.4 ± 8.0	63.3 ± 7.9	0.01*
Cost (J kg^{-1} m^{-1})	0,21	8,0	0,59	22,2	0,92	2.64 ± 0.71	2.65 ± 0.71	0,837
Efficiency (%)	2,17	11,0	6,02	30,4	0,87	19.6 ± 5.6	20.0 ± 6.0	0,647

SEM, standard error of measurement; SEM%, coefficient of variation of the SEM; MDC_{95}, minimal detectable change using a 95% confidence interval; MDC_{95}%, coefficient of variation of the MDC_{95}; ICC, intraclass correlation coefficient.

*P<0.05; **P<0.005.

[a]Positive and negative kinematic transversal values represent respectively internal and external rotation.

[b]Values are mean ± SD or median [P25;P75].

[c]Not meaningfully interpretable.

Discussion

This study describes the use of 3DGA to assess global musculoskeletal function in adults with haemophililia. Our results report a good reproducibility in regard to spatiotemporal parameters, kinematic (sagittal and frontal planes), kinetic, mechanical, and energetic gait variables. The intersession comparison revealed an unexpected infraclinical deterioration of gait pattern over a short time period of 18 weeks.

To optimize haemophilia treatment strategies, an accurate musculoskeletal function assessment is essential in order to diagnose haemophilic arthropathy, initiate strategies to treat or prevent progression of joint disease, assess treatment response, and compare outcomes of various treatment strategies [30]. Haemophilic joint status is traditionally evaluated using several clinical [4,7] or radiographic scoring systems [2,3,6]. Nevertheless, these scores are not sensitive enough to detect early changes in patients with little or absent joint damageas well as changesin patients with established arthropathy [3,6]. The summation of clinical or radiological individual joint scores may not be sensible, as the summation of ordinal figures does not provide an actual magnitude [26]. In conclusion, there is a lack of appropriate instruments for accurately measuring global musculoskeletal function in patients with haemophilia.

Gait analysis as a joint assessment tool in patients with haemophilia

Most likely because of recruitment difficulties, relatively few studies have focused on gait disorders in patients with haemophilia. Using ultrasound motion analysis allowing for kinematic measurement of the tibiotalar and subtalar joints, Seuser [31] reported the first study evaluating the efficacy of a conservative orthopedic treatment in patients with ankle arthropathy. More recently, Stephensen *et al.* [32] published the first 3DGA study integrating both kinematic and kinetic variables in children with haemophilia. Although focused only on the sagittal plane, the authors reported significant changes in kinematics and kinetics in children with haemophilia in comparison with age-matched healthy controls. Their results suggested that early biomechanical changes were present in children with a history of target joint, while lower limb joint function was more impaired than the current clinical evaluation suggested, confirming previous observations reported by Bladen *et al.* [33]. Using a simplified gait analysis system, the authors reported abnormalities in spatiotemporal parameters in asymptomatic children with haemophilia, and additional significant differences in children with established arthropathy.

Evaluation of natural progression of haemophilic arthropathy by gait analysis

Progression of 3DGA variables over time has never been evaluated in patients with haemophilia. We hypothesized that musculoskeletal function in patients with haemophilia would remain stable over our relatively short interval of 18 weeks. This hypothesis was supported by the fact that the patients were evaluated in the same medical and experimental conditions. Unexpectedly, the comparison of 3DGA across the two time intervals revealed small but significant changes in some gait variables, revealing infraclinic deterioration of gait pattern over time. In addition to the significant changes, non-significant

changes with a *P* value close to 0.05 should also be considered as they may provide valuable information. At single joint level, 3DGA showed a minor but highly significant 3° increase of knee ROM during swing phase, and a trend towards joint moment and power increases at the hip and the knee levels. All of the 18 subjects suffered from ankle arthropathy (Table 1), and a deterioration of ankle function (characterized by a tendency towards power decrease at the propulsive phase of walking) was observed over time. These changes may be accounted for by an adaptation of the knee and hip to ankle function deterioration. The most relevant change overall was a 2.1% decrease in recovery. The efficacy of gait's mechanisms can be quantified by the recovery index, which represents the energy transferred between potential and kinetic energies while walking. Abnormal movements of body segments due to lowest level gait disorders, such as musculoskeletal disorders, influence the motion of the CoM while walking. To the best of the authors' knowledge, only few studies have assessed mechanical work while walking, enabling the calculation of the recovery index [14]. As suggested by Detrembleur *et al.* [15], our findings imply that the calculation of the recovery index, and by extension the study of 3D motion of the CoM, may be an integrative indicator of the progression of gait pattern under pathological conditions.

Reproducibility of gait analysis in patients with haemophilia

Reproducibility studies of assessment tools are necessary to ensure that the error involved in measurement is small enough to allow for the detection of actual changes [25]. The reproducibility of 3DGA has been primarily based on studies on healthy subjects [34] with little exploration performed in patients populations. To date, no study has evaluated the reproducibility of 3DGA in patients with haemophilia.

This study supports and extends results of previous work, stressing the high reliability of mechanical and energetic variables. Similar recovery, cost, and efficiency ICC values have previously been reported in healthy children, children with cerebral palsy, and adult patients after stroke [13,16]. In addition, we found excellent reliability of spatiotemporal parameters, in line with similar ICC values reported in Alzheimer's disease patients [17]. Concerning joint kinematic, our study confirmed the same trends as reported in the review by McGinley *et al* [35], namely a high reliability of ankle, knee, and hip kinematic in the sagittal and frontal planes, and a poor reliability for the hip in the transverse plane, and pelvis in the three planes. The poor reliability of pelvic kinematic in the three planes along with lower limb kinematic in the transverse plane was reported in a previous study [36]. With regard to the joint moments and powers, the ankle power at push-off phase was fairly reproducible, whereas the power generated by the knee and the hip showed slight variation. Reliable reports did not always coincide with agreement results. Despite excellent reliability scores (ICC=0.91), the knee maximum flexion at loading response exhibited moderate agreement, with a SEM%=18%. Reliability parameters are dependent on between-subjects variance. The

great amount of homogeneous values in the population sample for the variable might explain the lower ICCs, whereas heterogeneity in the sample would have resulted in higher ICCs.

Calculation of error magnitude with the mean of MDC enables the minimization of the risk of over-interpreting small differences for a same subject evaluated twice as meaningful, and allows us to have greater confidence that a real improvement/deterioration exceeds the measurement error [35]. The calculation of MDC% suggests that some 3DGA variables (spatiotemporal parameters, kinematic ROM in sagittal plane, mechanics, and energetic) are better suited for detecting real changes in gait pattern in haemophilia subjects than other 3DGA measures (kinematic in transverse plane and joint position at heel strike). Whether the MDC values are sufficiently low will be related to the magnitude of the expected intervention effect size context. Surgical intervention such as a knee replacement is likely to induce changes superior to MDC in numerous gait variables, whereas more conservative approaches (such as use of NSAID) could induce actual but more subtle gait modifications, resulting in differences inferior to MDC values. We calculated the MDC with a confidence interval of 95%; however, an MDC_{90} or less could be selected, depending on the precision needed for the score estimate. Because of its capacity to detect small but significant changes even in relatively short intervals, 3DGA appears to be a powerful tool to assess abnormal gait patterns in cohort studies. Our findings, however, need to be confirmed using longer follow-up and larger population samples.

Our overall strong reproducibility results may be explained to some extent by the strictly similar medical and experimental conditions that the subjects were evaluated under, at the same spontaneous treadmill speed and the high number (n=10) of gait cycles averaged for each 3DGA trial. Some of the error measurements were probably inherent to our patient population. Poor results of pelvic kinematic may be explained to some extent by the difficulty in finding pelvic and femoral anatomical landmarks in some of our overweight subjects. The overall poor reproducibility of transverse plane kinematic may be explained by a potential inconsistency in the alignment of reflective markers on the thighs and legs.

Our study has some limitations. The choice of a mean time interval of 18 weeks was practical: 3DGAs were performed the same day as other medical consultations. Ideally, a 3DGA reproducibility study would include between-session intervals that are far apart, in order to minimize bias effects such as memorization of the reflective marker position. In contrast, longer time periods as adopted in our study increase the possibility that real change has occurred within the 3DGA interval, potentially introducing disease progression bias [35]. Inter-session comparison confirmed a systematic error induced by natural disease progression. Nevertheless, we decided to perform the reproducibility study for two main reasons. First, the systematic error induced by disease progression was not taken into account in the agreement study, as SEM calculation relies on the residual variance, thus including only unsystematic factors in contrast with “real” change. Moreover, as suggested

by intersession comparison results, the systematic changes due to disease progression were actual though subtle, and should consequently induce only a slightly underestimation of ICCs. Second, the principal aim of our reproducibility study was not to focus on raw reproducibility scores, but rather to establish a hierarchy of 3DGA variables to be considered either with confidence or distrust for future clinical research.

Conclusion

To our knowledge, this is the first study to document the natural progression of haemophilic arthropathy. Using a population of haemophiliac adults with established arthropathies, our results revealed an unexpected infraclinical deterioration of gait pattern over a short time period, as well as a tendency towards segmental joint adaptation in response to progressive joint function deterioration. Clinical gait analysis is therefore a powerful tool to assess abnormal gait patterns and the effects of disease progression in patients with haemophilia. Gait analysis is sufficiently reproducible in regard to spatiotemporal parameters, kinetic, mechanical, and energetic gait variables. The kinematic variables were only reproducible for the ankle, knee, and hip ROM in the sagittal and frontal planes.

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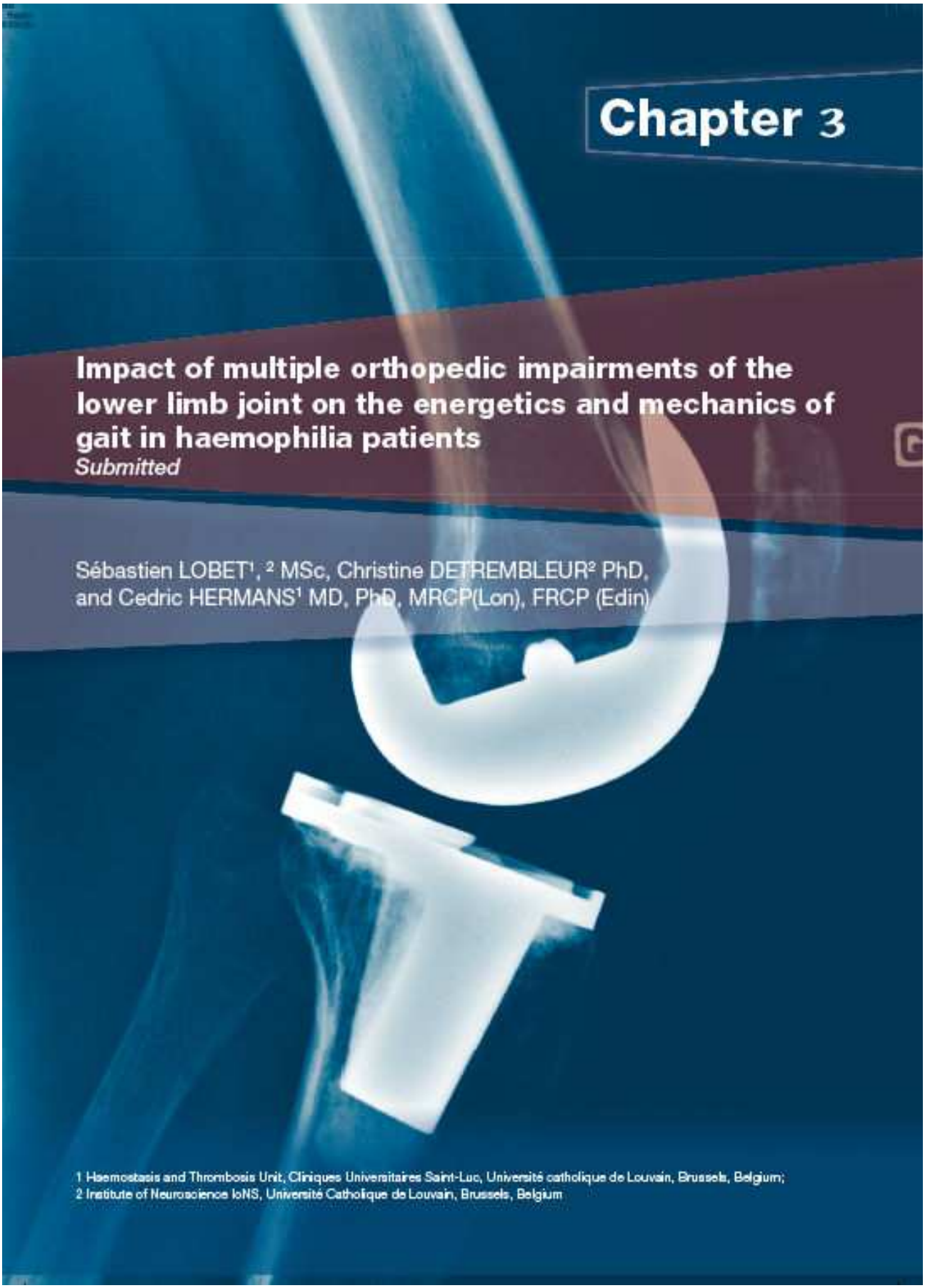

Chapter 3

Impact of multiple orthopedic impairments of the lower limb joint on the energetics and mechanics of gait in haemophilia patients

Submitted

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Abstract

Few studies have assessed the changes produced by multiple joint impairments (MJI) of the lower limbs on gait. In the context of MJI associated with systematic diseases or multiple traumas, quantifiable outcome measures are necessary if treatment benefits are to be compared. This study used three-dimensional gait analysis to investigate the kinematics, cost, mechanical work, and efficiency of walking in 31 haemophilia patients with MJI, with the results being compared with speed-matched values from a database of healthy subjects. Regarding energetics, the mass-specific net cost of transport (C_{net}) was significantly higher for MJI patients compared to control and directly related to a loss in active joint range of motion. Surprisingly, however, there was no substantial increase in mechanical work, with MJI patients being able to adopt a walking strategy to improve energy recovery via the pendulum mechanism. This probable compensatory mechanism to economize energy likely counterbalances the supplementary work associated with an increased vertical excursion of center of mass and lower efficiency of locomotion.Metabolic variables were probably the most representative variables of gait disability for subjects with complex orthopedic degenerative disorders.

Introduction

Three-dimensional gait analysis (3DGA) has allowed researchers and clinicians to better understand biomechanical alterations in patients with isolated lower limb osteoarthritis (OA) or joint replacement. However, few studies have assessed the changes produced by multiple joint impairments (MJI) of the lower limbs. In MJI associated with systematic diseases or multiple traumas, quantifiable outcome measures are necessary if treatment benefits are to be compared.

Generally, 3DGA focuses on segmental abnormalities, such as kinematics. Nevertheless, by comparing the mechanical work requirements and metabolic cost of walking, it is possible to evaluate thepenalty of these segmental abnormalities on overall locomotion function and determine the efficiency of mechanical work production. The total mechanical work (W_{tot}) may be obtained by calculating the amount of mechanical energy produced due to the energy changes of the center of mass (CoM)of the body relative to the ground (external work, W_{ext}) and kinetic energies of the lower limbs relative to the CoM (internal work, W_{int})[1]. This mechanical approach allows for calculating the recovery index, *i.e.*, the subject's ability to save energy by passively converting kinetic energy into gravitational potential energy and back again, similarly to an inverted pendulum [2]. In unilateral pathologic orthopedic conditions, such as knee OA [3;4], ankle OA [5], total knee replacement (TKR) [4], and ankle prosthesis [5], increased metabolic cost was reported, being partially attributed to increased W_{tot}.

Haemophilia patients are unique in the study of the functional alterations caused by severe MJI in association with OA and multiple orthopedic surgeries. The major complications in patients with this inherited coagulation disorder involve recurrent bleeding episodes into the joints and muscles. Over time, these bleeding episodes lead to soft tissue fibrosis, cartilage damage, and synovial hypertrophy, which gradually destroy the joints in relatively young patients [6].

This study was primarily aimed at observing the metabolic cost, mechanical work, and efficiency of walking among MJI subjects. Patients with restricted joint function walk slower [7;8], which was shown to reduce joint load [9] and maintain metabolic power within the normal physiological range [10]. Data relating to changes in walking speed is thus essential for identifying gait alterations caused by pathological processes, as opposed to changes arising from the slower spontaneous speed.Consequently, we performed 3DGA in haemophilia patients with MJI and compared the results with speed-matched values from a database of healthy subjects. Our initial hypothesis was that MJI would increase the vertical displacement of the CoM, thus inducing a rise in W_{ext}, which would increase metabolic cost. Given this context, the study's secondary aim was to investigate the relationship between joint damage and any changes in mechanical and energetic variables. We assumed that the

deterioration of gait pattern in MJI subjects correlated with the degree of impaired joint function and a reduction in active joint range of motion (ROM).

Materials and methods

Participants

Thirty-one haemophilia patients were enrolled, with characteristics provided in Table 1. All patients presented severe lower limb MJI, although they were capable of independent gait. Exclusion criteria comprised comorbidities with an impact on walking, such as neurological and cardiopulmonary diseases.The study protocol was approved by the institutional ethics committee, with all participants giving informed consent.

Table 1. Characteristics of the study group (*n*=31)

Age (years)	40 ± 9 (22-61)
Weight (kg)	82 ± 15 (57-126)
Height (m)	1.77 ± 0.07 (1.65–1.87)
BMI (kg/m^2)	26 ± 5 (19-40)
Hemophilia A/B	(28/3)
Factor deficiency (severe/moderate/mild)	(27/4/0)
Clinical assessment	
Total clinical score for the six lower limb joints (max. individual score = 68 pts)	15 ± 7 (2-32)
Mean affected joints/patient	3.1 ± 0.9 (1-5)
Lower limb articular status	
Unilateral ankle OA	1
Unilateral ankle OA + unilateral knee OA	1
Unilateral ankle OA + bilateral knee OA	1
Bilateral ankle OA	9
Bilateral ankle OA + unilateral knee OA	5
Bilateral ankle OA + bilateral knee OA	3
Bilateral ankle OA + unilateral TKR	4
Bilateral ankle OA + bilateral TKR	4
Bilateral ankle OA + unilateral knee OA + unilateral TKR	1
Bilateral ankle OA + bilateral TKR + unilateral THR	2
TOTAL	**31**

Values are mean ± SD (range)

BMI: Body Mass Index; OA: osteoarthritis; TKR: total knee replacement; THR: total hip replacement

Clinical assessment

MJI subjects were assessed using the physical examination part of the World Federation of Hemophilia joint score[11]. This scoring system was based on seven components, (joint ROM, flexion contracture, joint instability, swelling, muscle atrophy, axial deformity, crepitus with motion) pertaining to the lower limb joints. The maximum score was 12 for the ankle and knee and 10 for the hip, indicating the most pronounced OA. The

scores obtained at the ankle, knee, and hip levels were added together to determine the total clinical score for both lower limbs, ranging from 0 to 68.

Gait assessment

Gait was assessed using 3DGA, including spatiotemporal, kinematic, mechanical, and metabolic measurements. The reproducibility was previously validated [12]. MJI subjects walked at a self-selected speed (4.0±0.8 km h^{-1}, range 2.0–5.3 km h^{-1}) on a treadmill mounted on 3D force transducers [13]with neutral running shoes (Kalenji success Decathlon®, Villeneuve d'Ascq, France). Segmental kinematics were measured using the Elite-V5 system (BTS, Italy) at a sampling rate of 100 Hz. Six infrared cameras measured the coordinates of reflective markers to compute the angular displacements of the pelvis, hip, knee, and ankle joints [14]. Spatiotemporal parameters were assessed using 3D coordinates. The active ROM of the hip, knee, and ankle was calculated as follows:

- Ankle: A3-A2 (A3-maximum plantar flexion at push-off; A2-maximum dorsiflexion in stance);
- Knee: K4-K3 (K4-maximum flexion in swing; K3-maximum extension at pre-swing);
- Hip: H2-H1 (H2-maximum extension in stance; H1-flexion at initial contact).

W_{int} was calculated from kinematics data [15]. The body was divided into seven rigid segments. The internal mechanical energy of these segments corresponded to the sum of their rotational and translational energies due to their movements relative to the CoM. The W_{int} of each lower limb and HAT segment was calculated separately as the sum of the increments of the respective internal mechanical energy curves. W_{int} corresponded to the sum of work required to move the lower limbs and HAT segment.

W_{ext} and recovery index were computed according to Cavagna and Willems *et al.* [2;15]. The accelerations of CoM were computed from the 3D components of the ground reaction forces and mass of the subject. The mathematical integration of the accelerations provided the CoM velocity changes in three directions. From the instantaneous velocities and body mass, vertical, forward, and lateral kinetic energies of CoM were computed. A second mathematical integration was performed to determine the vertical displacement of CoM (S_v). The amplitude of the S_v was measured as the peak-to-peak amplitude over a stride. The increments of kinetic energies and gravitational potential energy curves represented, respectively, the positive work necessary to accelerate and to lift the CoM during a stride. W_{ext} was obtained by summing the increments of external energy over a stride. W_{tot} was calculated as the sum of W_{ext} and W_{int}.

Oxygen consumption was measured using ergospirometry (Quark b^2, Cosmed, Italy). The mass-specific net cost (C_{net}) was calculated by dividing the net energy consumption by

the walking speed. The efficiency of work production by the muscles was calculated as the ratio of W_{tot} and C_{net}[1].

Each session began with a rest period. Subjects were then asked to walk at their preferred speed for a few minutes until a steady state was reached and maintained for at least 2 min. Energetic variables were measured for 2 min. Kinematics were recorded for 20 sec and averaged for 10 successive strides. Means were used for statistical analyses.

Transformation of gait data into Z-score

As walking speed was shown to influence gait variables [16], individual patient values were compared to a dataset of normal values and then normalized to Z-score (Z) in order to identify MJI-caused gait alterations, as opposed to changes arising solely from the different speeds of subjects. Normal values were established in a control group of eight healthy subjects (mean age 29±16years; weight 65±10 kg; height 1.74±0.05 m) at six pre-determined speeds (1–6 km h^{-1}) following the method illustrated in Figure 1. Patient data was speed-matched with the means of the control group and normalized to Z (Fig. 1). For joint ROM, the mean values for both sides were used for calculating Z. One-sample t-test or Wilcoxon signed-rank test (non-normally distributed variables) against zero was used to compare subjects' Z-transformed gait variables with normal values (corresponding to Z=0).

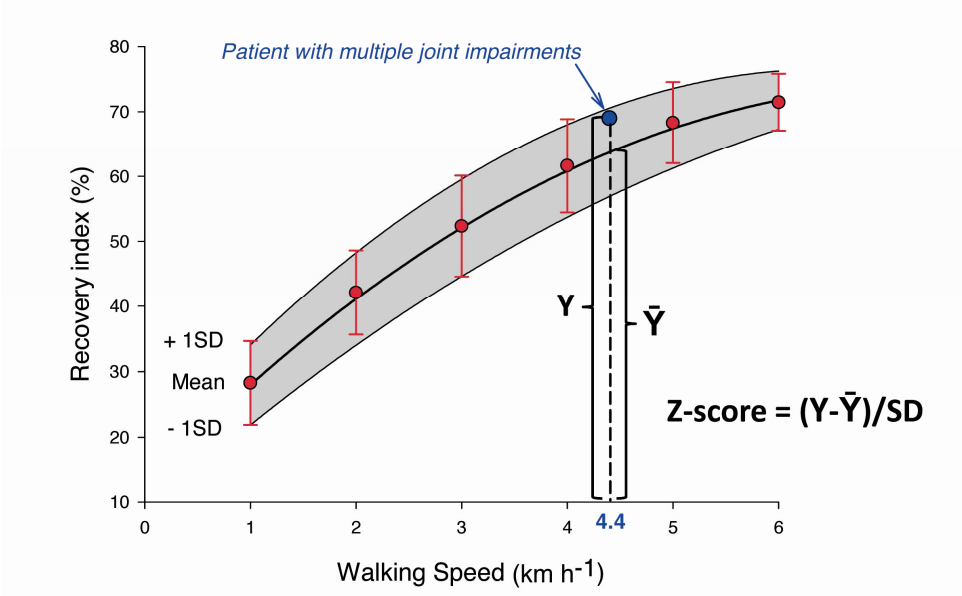

Fig. 1. An example of three-dimensional gait analysis variables expressed as a function of walking speed in the control group. Means and standard deviations (SD) for the recovery index were obtained for eight healthy subjects at each of the six pre-determined speeds (1 to 6 km h^{-1}). A quadratic extrapolation was then applied to the six mean and SD values, which allowed us to compare a patient walking at 4.4 km h^{-1}, for example, with the mean control value at the same speed. The Z-transformation was derived by subtracting the population's mean from the individual raw score, then dividing the difference by the population SD.

Relationship between 3DGA and joint damage extent

To establish the relationship between gait variables and MJI severity, all variables underwent principal component analysis (PCA). This method aimed to reduce the dimensionality of the data set and identify new meaningful underlying variables. PCA was performed on 11 non-redundant variables: total clinical score, number of affected joints (arthropathy count: 0-6), walking speed, Z-cadence, Z-W_{ext}, Z-W_{int}, Z-recovery, Z-C_{net}, Z-ankle, knee and hip ROM. The Kaiser-Meyer-Olkin value was 0.69, exceeding the recommended value [17], while Bartlett's sphericity test [18] reached statistical significance, supporting the factorability of the correlation matrix.

PCA revealed three components, explaining 32%, 21%, and 17% of the variance. For the interpretation of these components, orthogonal rotation (Varimax) was performed. Finally, the first three components were given a meaning and labeled. Only variables with the highest correlation to each component (factor loading, $r \geq 0.7$) were considered in determining what each component measured. Statistical analyses were performed using SigmaStat (v2.0) and SPSS (v15.0), with the significance level set at 0.05.

Results

Comparison between MJI and control

Results are shown in Table 2. Regarding kinematics, MJI subjects demonstrated a statistically significant reduction in ankle ROM (Z=-2.54; $P<0.001$) and hip ROM (Z=-0.66; $p<0.001$). At the knee level, MJI subjects showed only a trend towards reduced flexion ROM in swing phase (Z=-0.52; $P=0.054$).

In the MJI group, W_{ext} revealed a slight significant reduction (Z=-0.38; $P=0.049$), while W_{int} was similar in both groups (Z=-0.37, $P=0.256$). Consequently, there was a trend towards a minor W_{tot} reduction in the MJI group (Z=-0.37; $P=0.109$). Unexpectedly, the efficacy of the pendulum-like mechanism was significantly higher in MJI patients compared to control (Z=0.64; $P<0.001$), although subjects exhibited higher S_v (Z=0.99; $P<0.001$). C_{net} was also significantly higher in MJI patients (Z=2.71; $P<0.001$). This difference in C_{net}, combined with the unchanged between-group W_{tot}, resulted in a lower muscle efficiency of locomotion (Z=-1.10; $P<0.001$).

Table 2. Results of the statistical test on the normalized energetics and mechanics variables (Z-scores) for the hemophila group and absolute values mean for the haemophilia group and speed-matched control group

Gait variables	Z-score		Absolute values mean[c]		
	Multiple Joint Impairment group[a]	p-value[b]	(unit)	Multiple Joint Impairment group[a]	Control group
Kinematics					
Mean ankle sagittal ROM at push-off phase	**-2.54 ± 0.67**	**<0.001**	(°)	15.0	27.7
Mean knee ROM in swing phase	-0.52 ± 1.44	0.054	(°)	55. 6	60.1
Mean hip sagittal ROM	**-0.66 ± 1.08**	**<0.001**	(°)	42.8	45.9
Mechanical work / Energetics					
W_{ext}	**-0.38 ± 1.04**	**0.049**	(J kg^{-1} m^{-1})	0.245	0.261
W_{int}	-0.37 [-0.99;0.39]	0.256	(J kg^{-1} m^{-1})	0.255	0.259
W_{tot}	-0.37 ± 1.25	0.109	(J kg^{-1} m^{-1})	0.500	0.520
Recovery	**0.64 ± 0.84**	**<0.001**	(%)	64.7	60.2
S_v	**0.99 ± 1.32**	**<0.001**	(m)	0.034	0.028
C_{net}	**2.71 ± 2.01**	**<0.001**	(J kg^{-1} m^{-1})	2.73	1.96
Efficiency	**-1.10 ± 0.81**	**<0.001**	(%)	19.7	27.2

Abbreviations: ROM: range of motion; W_{ext}: external mechanical work; W_{int}: internal mechanical work; W_{tot}: total mechanical work; S_v: vertical centre of mass displacement; C_{net}: mass-specific net cost of transport

[a]Z-score is expressed as mean ± SD (one sample t-test) or median [P25 ; P75] (one sample Wilcoxon signed-rank test)

[b]p-value indicates if the Z-score significantly differed from 0: One-sample t-test (normally distributed values) OR one-sample Wilcoxon signed-rank test (non-normally distributed values)

[c]As Z-value was a dimensionless quantity, the gait variables in both groups were also expressed in their original units for better readability. Absolute value means for each variable are therefore strictly indicative as these values represent the mean of raw data of patients/controls walking at different self-

Relationship between 3DGA and joint damage extent

The first component determined by PCA was labeled “joint status”, the second “metabolic cost”, and the third “W_{ext}”. Figure 2 represents the factor loading of each variable with these three components, with grey rectangles indicating the variables significantly correlating with the component (r≥0.7). Total clinical score (r=0.73), arthropathy count (r=0.72), walking speed (r=-0.83), Z-cadence (r=0.83), and Z-W_{int} (r=0.74) loaded on the first component. Z-C_{net} (r=-0.81) loaded on the second component with Z-ankle ROM (r=0.73) and, to a lesser extent, with Z-knee ROM (r=0.66), while Z-W_{ext} (r=0.83) loaded with Z-recovery (r=-0.84) on the third component.

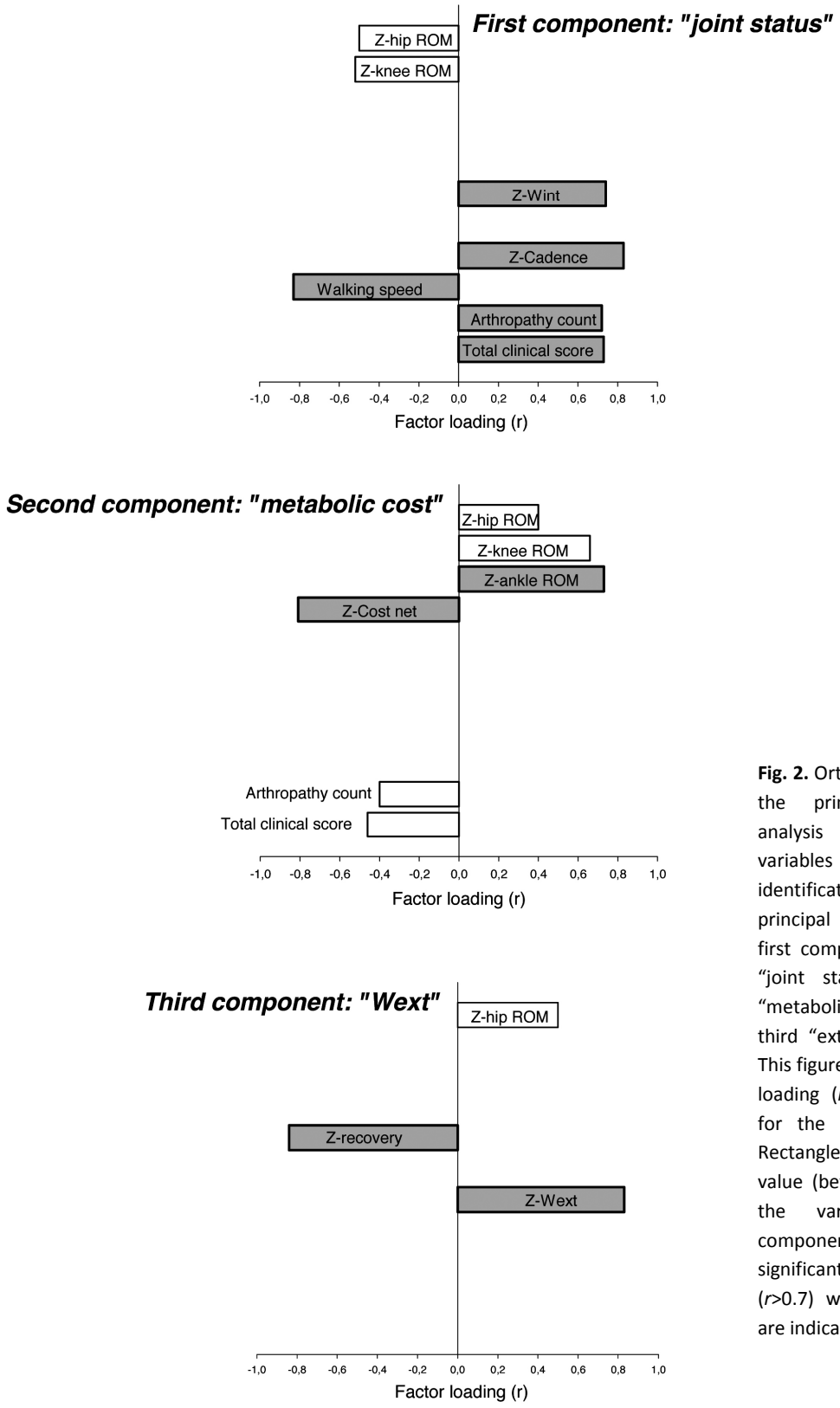

Fig. 2. Orthogonal solutions in the principal component analysis of the selected variables allowed for the identification of three principal components. The first component was labeled "joint status", the second "metabolic cost", and the third "external work (W_{ext})". This figure presents the factor loading (*r*) of each variable for the three components. Rectangles indicate the *r*-value (between -1 and 1) of the variable with the component. The variables significantly correlating ($r>0.7$) with the component are indicated in grey.

Discussion

Our aim was to assess the impact of MJI on cost, mechanical work, and walking efficiency, while taking into account the effect of walking speed. Our results suggested that MJIsubjects exhibited a major increase in C_{net} and decrease in gait efficiency as compared to normal subjects. Surprisingly, these changes were associated with mechanical work in the normal range and more efficient pendulum mechanism.

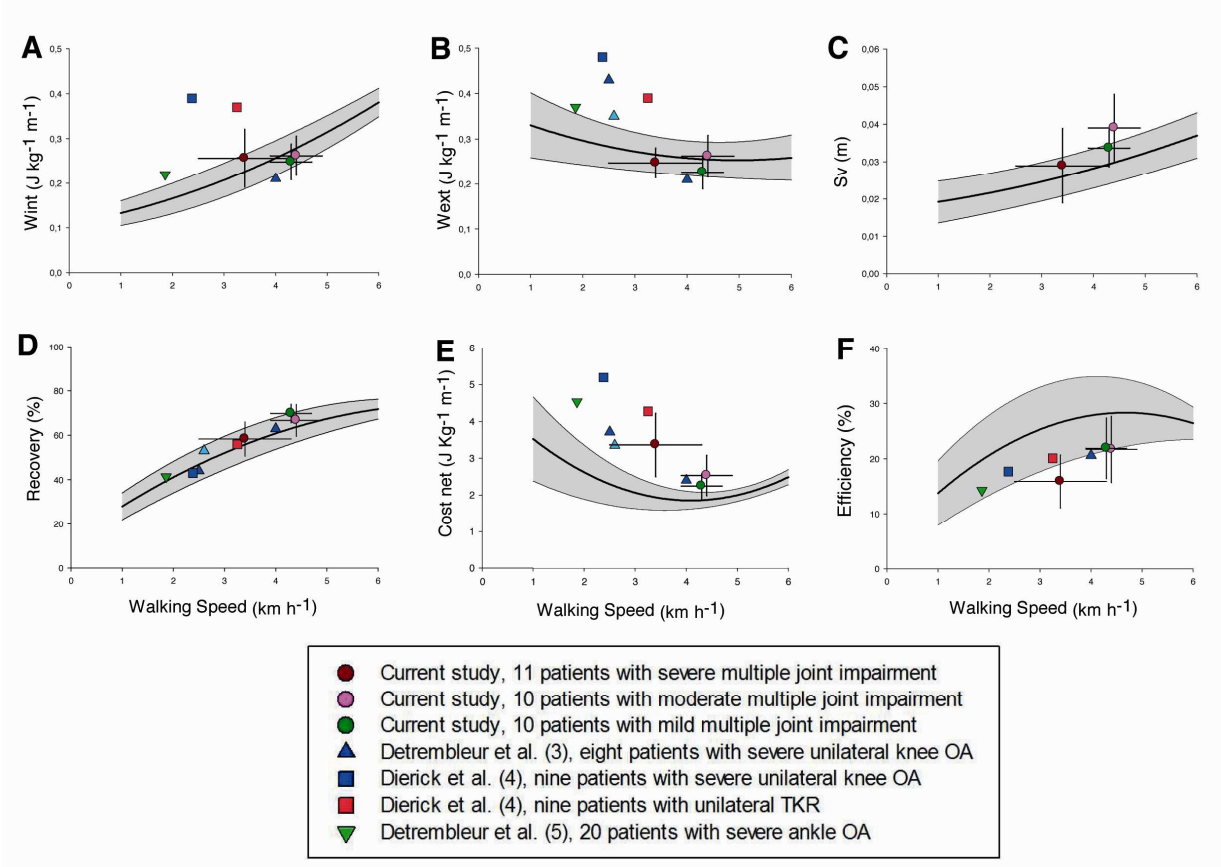

Fig. 3. Mean internal mechanical work (W_{int}) (A), external mechanical work (W_{ext}) (B), vertical displacement of the centre of mass (S_v) (C), recovery index (D), net metabolic cost (E), and efficiency of mechanical work production (F) plotted as a function of walking velocity for our study patients (circles) in addition to other studies involving unilateral orthopedic disorders (squares and triangles). Horizontal and vertical bars (given only for our study) represent the standard deviation of self-selected walking speeds and gait variables.

OA: osteoarthritis; TKR total knee replacement

Cost and vertical displacement of CoM

MJI subjects expended more energy when walking at a given speed than healthy subjects. Our observed increase in C_{net} (Z=2.71) was in accordance with the results for

patients with unilateral ankle [5] and knee [3;4] end-stage OA, which also reported increased C_{net} compared to normal (Fig. 3E).

Regarding the influence of CoM displacement, Kerrigan *et al.*[19] demonstrated that S_v reliably predicted oxygen consumption during walking. Our results confirmed the increased S_v (Z=0.99) of MJI subjects, which partially explains the increased C_{net}. The reasons for increased S_v were probably that all of our subjects presented ankle OA and significantly reduced ROM during push-off, while it was previously shown that ankle ROM, and particularly heel rise, have a primary role in reducing S_v, by up to two-thirds of the total reduction [20].

When the severity of MJI subjects was arbitrarily classified as "mild" (uni/bilateral ankle OA, *n*=10), "moderate" (uni/bilateral ankle OA + unilateral knee OA/TKR, *n*=10), and "severe" (at least bilateral knee OA/TKR, *n*=11), a progressive increase in C_{net} as a function of impaired joint status was observed. This could be explained by the fact that, regarding the second component of PCA, C_{net} was inversely correlated with lower limb joint ROM. Such ROM are certainly more limited in patients with more severely impaired joints. One would also expect the increase in S_v to be proportional to the severity of the impairment, which was partially verified by our results, as subjects with moderate MJI had a higher S_v than those with mild MJI (Fig. 3C). However, the more severely impaired subjects did not exhibit the highest S_v. *A posteriori* ANOVA with Holm-Sidak post-hoc tests revealed that severely affected subjects had significantly increased knee angle at heel strike compared to moderate and mild subjects (14.1° *vs.* 7.5° and 5.2°, respectively). The flexed-knee pattern of subjects with bilateral knee impairment was already shown to have excessively smooth S_v, with consequently increased metabolic energy expenditure as observed in normal subjects walking with knee flexion [21].

Efficacy of the pendulum mechanism and mechanical work production

As observed in Figure 3A and confirmed by the first PCA component, an increase in W_{int} was linked to a higher cadence and shorter stride length in the subjects with the most impaired joints. The decrease in joint ROM and subsequent decrease in angular speed probably limited the increase in W_{int} for severely affected subjects. Consequently, W_{int} remained in the normal range.

The overall elevation of S_v in MJI subjects should have resulted in increased W_{ext}, as more mechanical energy was needed to redirect the CoM vertically. However, W_{ext} was found to decrease slightly (Z=-0.38), which may be explained by the strategy of MJI subjects to conserve part of the muscle work and save energy via an efficient recovery index [1]. During walking, recovery attains a maximum at an intermediate speed when the difference

in amplitude of the potential and kinetic energy curves approaches zero and the phase difference between the energy curves approaches 180° [2]. An increased recovery index in the MJI group may therefore be explained by the relative amplitude of the potential and kinetic energy curves, their shape, and relative phase [22]. Further information about the pendulum mechanism of walking may be obtained by analyzing how the pendulum mechanism occurred during the cycle (instant recovery) [22]. Although additional investigations are needed, it could be assumed that MJI patients increase their recovery because of the higher amplitude of potential energy induced by increased S_v or a better phase difference between potential and kinetic energies.

The third PCA component confirmed that the W_{ext} and recovery values were inversely correlated, but independent from joint status and C_{net}.A recovery index in the normal range was previously reported in patients with isolated orthopedic disorders [3-5] (Fig. 3D). However, contrary to MJI subjects, patients with unilateral OA showed a significant increase in W_{ext} (Fig. 3B). These patients were in a pre-surgery situation, *i.e.*, with a severe OA grade associated with acute pain. In contrast, our subjects were more chronic and stable, as they had joint replacements and/or sustained long-standing joint OA. Acute pain may therefore have predisposed these patients with end-stage OA to adopt compensatory gait alterations with a subsequent increase in W_{ext}, while preserving the pendulum mechanism. This is supported by the fact that the use of anti-inflammatory drugs in patients with end-stage unilateral knee OA tended to normalize W_{ext}[3]. These contrasting findings suggest that further investigations are necessary in order to characterize how acute joint pain alters gait pattern.

As a result of unchanged W_{int} and slightly reduced W_{ext}, the W_{tot} remained within the normal range, and thus, the elevated C_{net} reported could not be explained mechanically. However, these findings contradict previous studies on unilateral orthopedic conditions [3-5], which attributed the increase in C_{net} to higher W_{tot}. The discrepancy observed in our study may be explained by a possible underestimation of the W_{tot}. In fact, the co-contraction of antagonistic muscle groups was identified as a neuromuscular alteration associated with end-stage ankle [23] and knee OA [24;25]. However, frictional losses occurring mainly within antagonistic muscles working against each other during co-contractions would elicit a meaningful metabolic energy demand with no apparent net work [20;26].

An efficient locomotion involves most of the metabolic energy input being transformed into mechanical work [1;15]. In normal gait, the efficiency reached a maximum of 30-35% at 4.5 km h^{-1} [1;15]. In MJI subjects, as a result of the large increase in C_{net} and unchanged W_{tot}, the ratio of muscular efficiency was reduced to 20% (Table 2, Fig. 3F), probably due to co-contractions that were not measured in this study.

Limitations and perspectives

Contrary to previous studies [3-5;27], our study demonstrated that fluctuations in W_{ext} or W_{int} alone could not explain increased C_{net}.The increase in C_{net} may therefore be due to factors not accounted for in the calculation of W_{tot} in addition to methodological limitations in calculating W_{tot}[28]. Future studies should therefore investigate the metabolic importance of the co-activation of antagonistic muscles.

Conclusions

To our knowledge, ours is the first study to quantitatively describe the energetic and mechanical changes during gait as a result of MJI. We reported that C_{net} was greater in MJI patients and directly related to a loss in joint ROM. Surprisingly, however, there was no substantial increase in W_{tot}, with MJI patients being able to adopt a walking strategy to improve energy recovery. This probable compensatory mechanism to economize energy likely counterbalances the supplementary work associated with the increased vertical excursion of CoM. Metabolic variables were probably the most representative variables of gait disability for subjects with complex orthopedic degenerative disorders.

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Section 2

Haemophilic ankle arthropathy

Chapter 4

Impact of ankle osteoarthritis on the energetics and mechanics of gait: The case of haemophilic arthropathy

Clinical Biomechanics. In press

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Abstract

Background: Osteoarthritis may affect joints in any part of the body, including the ankle. The purpose of this study was to assess the impact of ankle osteoarthritis on the energetics and mechanics of gait, while taking into account the effect of slower speed generally adopted by patients with osteoarthritis.

Methods: Using a motion analysis system, synchronous kinematic, kinetics, spatiotemporal, mechanics and metabolic gait parameters were measured in 10 patients diagnosed with ankle osteoarthritis consecutive to haemophilia. The subjects walked at a self-selected speed and their performance was compared to speed-matched normal values obtained in healthy control subjects.

Findings: Speed-normalization using a Z-score transformation showed a significant increase in metabolic cost (Z=1.78; *P*=0.006)and decrease in mechanical work (Z=-0.97; *P*=0.009). As a consequence, muscular efficiency also decreased (Z=-0.97; *P*=0.001). These changes were associated with a surprising efficacy of the pendular mechanism*, i.e.,* an improved recovery index (Z=0.97; *P*=0.004).

Interpretation: Our findings suggest that patients with ankle osteoarthritis adopt a walking strategy which improves recovery through the pendular mechanism. This may be a compensatory mechanism in order to economize energy which would counterbalance the energy waste due to low muscle efficiency. These modifications are proportional to the impaired ankle function. Our data provides a quantitative baseline to better understand the dynamics of ankle osteoarthritis and determine the individual role that lower limb joints play in the multiple chronic joint affections.

Introduction

Ankle osteoarthritis (OA) is a progressive degenerative joint disease that is characterized by pain, functional disability, loss of autonomy, and altered quality of life in its end-stage [1]. In 70% of cases, ankle OA is post-traumatic and in 30% caused by primary OA or secondary to systemic diseases [2].

Few studies have examined the biomechanical effects of ankle OA, which may be due to the lower incidence of symptomatic ankle OA compared to knee and hip OA,as it occurs approximately nine times less frequently [3]. Ankle OA is a common complication of haemophilia, an inherited blood disorder causing recurrent episodes of intra-articular bleeding into the tibiotalar or subtalar joints that leads to the destruction of joint cartilage and irreversible chronic arthropathy [4].

Patients with restricted ankle function due to OA generally walk slower than normal [5;6], which has been shown to mediate joint load reduction [7] and maintain metabolic power in the normal physiological range [8]. Data relating to changes in walking speed is therefore essential to identify gait alterations caused by pathological processes, such as ankle OA, as opposed to changes arising solely from the slower spontaneous speeds of patients.

Previous biomechanical studies on ankle OA focused on segmental kinematic and kinetic abnormalities alone, providing little information about patients' gait limitations or disabilities [1;5;6]. These issues are better approached using mechanical and energetic measurements, such as metabolic cost and mechanical work, which are considered to be concise and integrative indicators of gait mechanics [9]. While restricted ankle range of motion (ROM) following arthrodesis, total ankle arthroplasthy (TAA), and OA typically increase metabolic energy expenditure [8;10-13], little is known about the reasons for this energetic increase.

The purpose of our study was to assess the impact of ankle OA on the energetic costs and mechanical work of level walking. The energy expended required during steady state normal walking is minimized when the body's centre of mass (CoM) follows a sinusoidal trajectory of low amplitude, but is dependent on several kinematic determinants: foot rockers, knee flexion in stance and swing, and pelvic rotation [14]. The most crucial gait determinant is the third foot rocker in association with heel rise, which explains up to 75% of the reduction in vertical CoM displacement in normal gait [15]. We therefore hypothesized that impaired ankle function due to OA would increase the metabolic cost of walking and increase mechanical gait parameters. Our cohort comprised a homogenous sample of patients with ankle OA secondary to haemophilia. Instrumented gait analysis was performed and compared to a healthy control sample, while taking into account the effect of speed.

Methods

Patient recruitment

Ten male patients (mean age 33 (SD 6) years; weight 76 (SD 12) kg; height 1.75 (SD 0.05) m) diagnosed with ankle OA secondary to haemophilia were recruited at the Haemophilia Comprehensive Center of the *Cliniques Universitaires Saint-Luc*, Brussels, Belgium. A total of 17 ankles were affected, which comprised seven patients with bilateral involvement and three unilateral. Exclusion criteria were orthopedic problems in the knee, hip, or pelvis in addition to neurological and cardiopulmonary impairments or other comorbidities that could affect walking.

The control group involved eight healthy subjects (mean age 29 (SD 16)years; weight 65 (SD 10) kg; height 1.74 (SD 0.05) m), with no history of orthopedic or neurological pathology affecting the lower limbs.

The study protocol was approved by the institutional ethics committee, and all participants gave their informed consent to participating in the study.

Gait analysis

Gait was assessed using three-dimensional gait analysis (3DGA), which included synchronous kinematic, kinetic, mechanic, and metabolic measurements. The accuracy and reproducibility of our method has been previously validated in normal and pathological gait [16-19]. Patients walked at a self-selected speed (4.3 (SD 0.3) km h^{-1}) on a treadmill mounted on 3D strain-gauge force transducers [17]. Segmental kinematics were recorded using the Elite system (Elite V5, BTS, Italy) at a sampling rate of 100Hz. Six infrared cameras measured the 3D coordinates of reflective markers positioned on specific anatomical landmarks (head of fifth metatarsal, lateral malleolus, lateral condyle, greater trochanter, iliac crest, sacrum and acromion) to compute angular displacements of the pelvis, hip, knee and ankle joints as described in detail by Davis *et al*. [20]. Spatiotemporal parameters were assessed using 3D position data. The net moments of force and power that were generated or absorbed at the major lower limb joint muscles in the sagittal plane were estimated by inverse dynamic.

Internal work (W_{int}), *i.e.*, the positive work performed by muscles in order to move the limbs relative to the body's CoM, was calculated from kinematics data [21]. The CoM of each body segment exerts a moment about an arbitrary origin and the sum of these moments can be replaced by a single body mass at the total body CoM. The body was divided into seven rigid segments: head–arm–trunk (HAT), thighs, shanks, and feet. The internal mechanical energy of the body segments corresponded to the sum of rotational and

translational energies of these segments due to their movements relative to the CoM. For each lower limb, the internal mechanical energy of the thigh, shank and foot were summed. As regards to the HAT segment, the internal mechanical energy was first calculated for the right and left segments comprised between the acromion and the great trochanter (considered as a rigid and homogenous segment) and then averaged in order to obtain HAT's mechanical energy. The W_{int} of each lower limb and HAT segment was then calculated separately as the sum of the increments of the respective internal mechanical energy curves. Finally, W_{int} during gait corresponded to the sum of the W_{int} (in J kg^{-1} m^{-1}) done to move the lower limbs and the HAT segment.

3D ground reaction forces were recorded using the strain gauges at 100 Hz (Pharos System Inc., USA). External work (W_{ext}), *i.e.*, the work performed to lift and accelerate the CoM relative to the surroundings, was computed following the method described in detail by Cavagna [22], validated by Willems *et al*. [21] and adapted to pathological gait [23]. The 3D accelerations of the CoM were computed from the vertical, lateral and forward components of the ground reaction forces and the mass of the subject. The mathematical integration of the 3D accelerations gave the velocity changes of the CoM in all three directions (V_v, V_f, V_l). From the instantaneous V_v, V_f and V_l and the body mass (M), we computed the instantaneous vertical ($E_{kv}=1/2MV^2_v$), forward ($E_{kf}=1/2MV^2_f$) and lateral ($E_{kl}=1/2MV^2_l$) kinetic energies of the CoM. A second mathematical integration of V_v was performed to determine the vertical displacement of the CoM (S_v). The amplitude of vertical CoM displacement was measured as the peak-to-peak amplitude on the S_v curve over a stride. The instantaneous gravitational potential energy ($E_p=MgS_v$) was computed from S_v, the body mass and the gravity constant (g). The total external mechanical energy (E_{ext}) of the CoM was calculated as the sum of E_{kf}, E_{kv}, E_{kl} and E_p. The increments of the E_{kf}, E_{kv}, E_{kl} and E_p curves represented, respectively, the positive work (W_{ekf}, W_{ekv}, W_{ekl} and W_{ep}, expressed per kilogram body mass and per distance travelled) necessary to accelerate the CoM in the three directions and to lift the CoM during a stride. W_{ext} was obtained by summing the increments of E_{ext} over a stride. W_v represents the work done against gravity and was the sum of W_{ekv} and W_{ep}. The total mass-specific muscular work per distance travelled (W_{tot}) was calculated as the sum of W_{ext} and W_{int} and expressed in J kg^{-1} m^{-1}.

The 'recovery' quantifying the percentage of mechanical energy saved via a pendulum-like exchange between gravitational potential energy and kinetic energy of the CoM was calculated as [21]:

$$Recovery(\%) = 100 \times \frac{W_{ekf} + W_{ekv} + W_{ekl} + W_{ep} - W_{ext}}{W_{ekf} + W_{ekv} + W_{ekl} + W_{ep}}$$

The rate of oxygen consumption was measured using an ergospirometer (Quark b^2, Cosmed, Italy). After a steady state was reached, metabolic data was collected. The mass-specific net cost of transport (C_{net}) was calculated by dividing the net energy consumption by

the walking speed. The efficiency of positive work production by the muscles during walking was calculated as the ratio of W_{tot} and C_{net}[24]. It is to note that the difference of body weight between the ankle OA and control groups (76 kg *vs.* 65 kg respectively) did not influence our results as kinetics, mechanical work and C_{net} were normalized by body weight.

Each session began with a rest period. Subjects were then asked to walk at their preferred speed for a few minutes until a steady state was reached and maintained for at least 2 min. Energetics variables were then measured for 2 min. Kinematics and kinetics were simultaneously recorded for 20 sec and then averaged for 10 successive strides. The mean of each value was used for statistical analysis.

Transformation of subjects' gait data into Z-score

As mentioned, the patients walked at self-selected speed on the treadmill. In order to determine the influence of speed and impact of ankle functional deficit on gait, individual patient values were normalized into Z-score (Z) for all of the 3DGA variables.

The same methodology of data acquisition was applied to the healthy subjects. The control group walked on the treadmill at six pre-determined speeds (1–6 km h^{-1}) and 3DGA variables were simultaneously recorded for each speed. The mean and standard deviation (SD) of the eight subjects (and eight right ankles by convention) were calculated for each of the 3DGA variables at the six pre-determined speeds. A linear or quadratic extrapolation was then fitted across the mean values (and SD) obtained at each speed in order to estimate the 3DGA values of the control group at various walking speeds (Fig. 1).

All patients' data were speed-matched with the mean values of the control group and then normalized into a Z-score (Fig. 1). The Z-transformation was derived by subtracting the population's mean from an individual raw score, then dividing the difference by the population standard deviation.

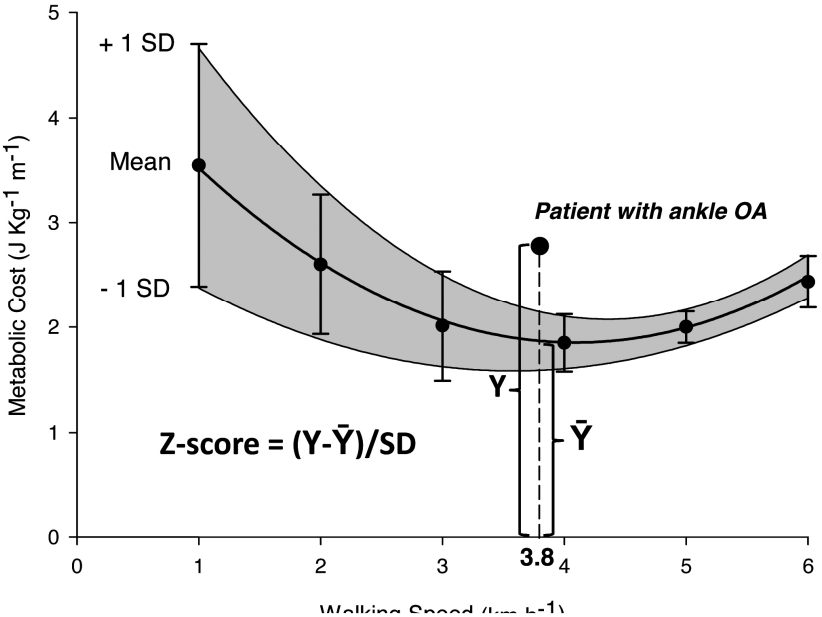

Fig. 1. Example of a 3DGA variable expressed as function of the walking speed in the control group. Mean and SD of the metabolic cost were obtained for the eight healthy subjects at each of the six pre-determined speeds. A quadratic extrapolation was then fitted across the six mean values and SD, which allowed us to locate and compare a patient walking at 3.8 km h^{-1}, for instance, with the mean value of the control group at the same speed. Z-score transformation was then applied.

Statistical analysis

In order to compare Z-transformed gait variables between patients and control group, one sample t-test (normally distributed variable) or one-sample Wilcoxon signed rank test (no normally distributed variable) against zero were used.As Z is a dimensionless quantity, the mean of each variable were also calculated in order to express the difference between the two groups in original units.

As a previous study reported, ankle power was the most representative 3DGA variable for ankle function [25]. The association between the Z-transformed ankle power and Z-transformed mechanical and energetic gait variables was then assessed using the Spearman rank correlation. All statistical analyses were performed with significance level at $\alpha = 0.05$ using SigmaStat software (v2.0 for Windows; Systat Software Inc., Chicago, IL, USA).

Results

Spatiotemporal, kinematic, and kinetic variables

The results for all tested parameters are shown in Table 1. There was no significant difference in cadence and step length between the ankle OA and control groups. The stance-phase duration was increased in the ankle OA group (median Z=1.15; *P*=0.012; 64.8% *vs.* 64.1% for the ankle OA and control groups, respectively).

Regarding kinematics and kinetics at the push-off phase, the ankle OA patients demonstrated a statistically significant reduction in sagittal ROM (third rocker) (Table 1 and fig. 2A) and peak power (Z=-2.55; *P*<0.001 and Z=-0.73; *P*=0.008, respectively) (Fig. 2C), while the maximum plantarflexion moment was increased (median Z=0.76; *P*=0.031) (Fig. 2B).

At the knee level, the OA ankle group showed no differences in flexion ROM at loading response (Fig. 2D). However, the peak extension moment decreased significantly during this period (Z=-0.82; *P*<0.001) (Fig. 2E). During the swing-phase, knee flexion ROM was slightly increased (Z=0.43; *P*=0.024) (Fig. 2D), while the peak eccentric power was reduced significantly (Z=-0.40; *P*=0.004) (Fig. 2F).

With respect to the hip, sagittal ROM was slightly reduced in the OA group (Z=-0.47; *P*=0.032) (Fig. 2G). No differences in the maximum extension moment (Fig. 2H) and peak positive power of hip extensors (Fig. 2I) were observed, although the moment (Fig. 2H) and powerof hip flexors (Fig. 2I) at early swing-phase were found to be significantly reduced in the OA subjects (Z=-0.90; *P*<0.001 and Z=-0.85 respectively; both *P*<0.001).

Mechanical work

In the ankle OA group, W_{int} was significantly reduced (Z=-0.74; *P*=0.005), while the change in W_{ext} did not reach statistical significance (Z=-0.61, *P*=0.085). As a consequence, there was a reduction in W_{tot} that was statistically significant (Z=-0.97; *P*=0.009) (Fig. 3B). Although the height of ankle OA patients compared to control was not statistically different (1.75 (SD 0.05) m*vs*1.74 (SD 0.05) m, *P*= 0,409), the amplitude of the vertical CoM displacement increased by about 0.5 cm (Z=0.88; *P*=0.022). Unexpectedly, the efficacy of the pendulum-like mechanism was higher in ankle OA patients compared to control, with the mean recovery in patients reaching 70% (Z=0.97; *P*=0.004).

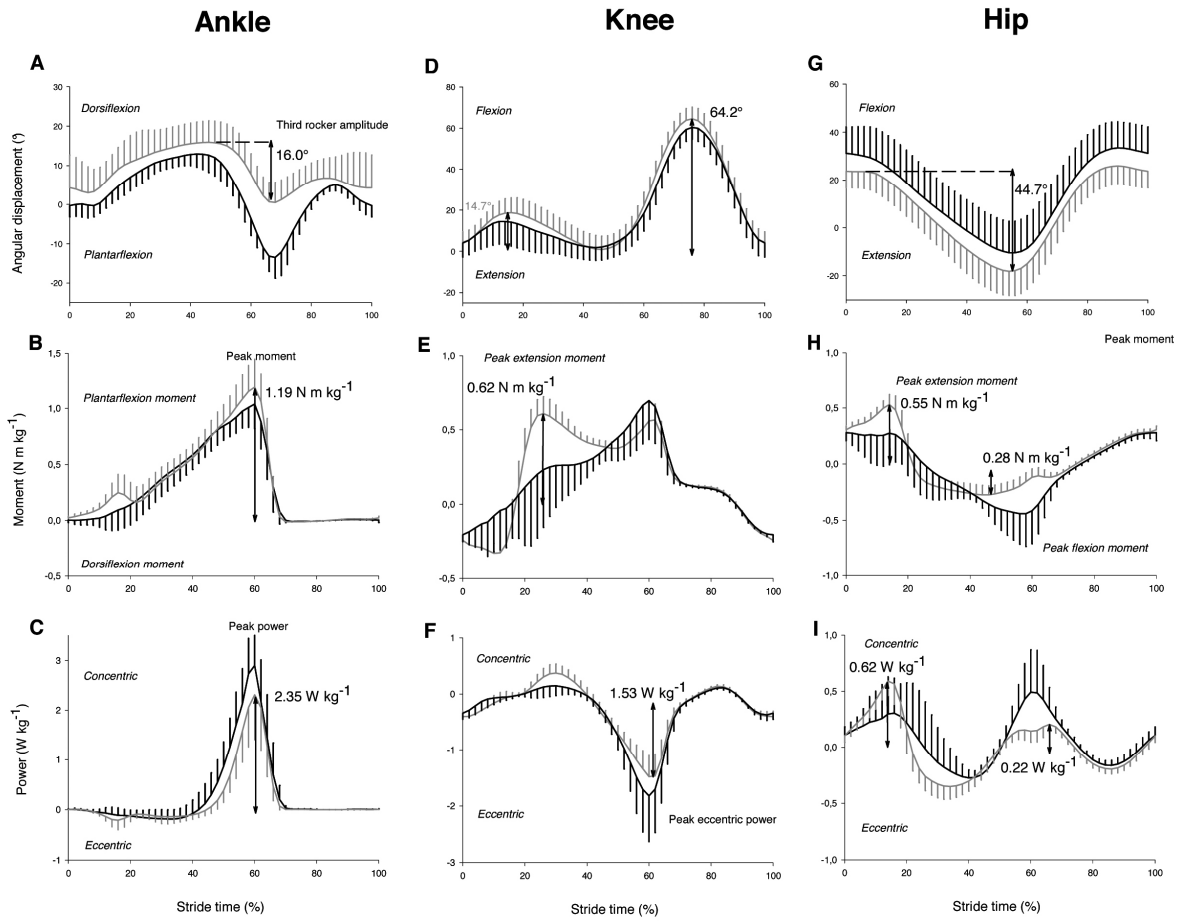

Fig.2. Sagittal ankle, knee and hip displacement, moment, and power as a function of the percentage of a walking stride. The gray symbols represent the mean of the 17 trials of the ankle osteoarthritis group (mean speed: 4.3 (SD 0.3) km h^{-1}). The black symbols represent the mean for the control group at 4 km h^{-1}(*n*=8). Vertical bars indicate standard deviations.

Metabolic variables

On average, C_{net} was 22% higher in ankle OA patients compared to control, which was statistically significant (Z=1.78; *P*=0.006; mean cost 2.29 *vs.* 1.87 J kg^{-1} m^{-1}) (Fig. 3A). As a result of the lower W_{tot} and higher C_{net}, overall muscle efficiency of locomotion was significantly decreased by 24% in ankle OA patients (Z=-0.97; *P*=0.001; mean efficiency 21.4 % *vs.* 28.0%) (Fig. 3C).

Table 1. Results of the statistical test on the normalized spatiotemporal, kinematics, kinetics, energetics and mechanics variables (Z-scores) for the ankle osteoarthritis group and absolute values mean for the ankle osteoarthritis group and speed-matched control group.

Gait variables[a]	Z-score		Absolute values mean[d]		
	Ankle OA[b]	*P*-value[c]	(unit)	Ankle OA	Control
Spatiotemporal parameters					
cadence	0.49 (1.03)	0.847	(step min^{-1})	109.9	109.5
step length	-0.46 (1.05)	0.092	(m)	0.72	0.75
stance phase duration	**1.15 [0.74;1.44]**	**0.012**	(% gait cycle)	64.8	64.1
Kinematics					
ankle sagittal ROM at push-off phase (third rocker)	**-2.55 (0.82)**	**<0.001**	(degree)	16.0	28.7
knee maximum flexion at loading response	0.40 (0.91)	0.088	(degree)	14.7	12.2
knee ROM in swing phase	**0.43 (0.71)**	**0.024**	(degree)	64.2	60.9
hip sagittal ROM	**-0.47 (0.82)**	**0.032**	(degree)	44.7	46.9
Kinetics					
ankle peak plantarflexion moment at push-off phase	**0.76 [0.23;1.48]**	**0.031**	(N m kg^{-1})	1.19	1.06
ankle peak power at push-off phase	**-0.73 (0.99)**	**0.008**	(W kg^{-1})	2.35	2.94
knee peak extension moment at loading response	**-0.82 (0.42)**	**<0.001**	(N m kg^{-1})	0.62	0.79
knee peak eccentric power at swing phase	**-0.40 (0.50)**	**0.004**	(W kg^{-1})	1.53	1.83
hip peak extension moment at early loading response	0.15 (0.39)	0.14	(N m kg^{-1})	0.55	0.53
hip peak flexion moment at early swing phase	**-0.90 (0.34)**	**<0.001**	(N m kg^{-1})	0.28	0.51
hip peak positive power of extensors at early loading response	-0.11 (0.41)	0.302	(W kg^{-1})	0.62	0.65
hip peak positive power of flexors at early swing phase	**-0.85 (0.23)**	**<0.001**	(W kg^{-1})	0.22	0.53
Mechanical work / Energetics					
W_{ext}	-0.61 (0.99)	0.085	(J kg^{-1} m^{-1})	0.23	0.26
W_v	**1.54 (1.22)**	**0.003**	(J kg^{-1} m^{-1})	0.44	0.37
Vertical CoM displacement	**0.88 (1.01)**	**0.022**	(m)	0.034	0.029
W_{int}	**-0.74 (0.63)**	**0.005**	(J kg^{-1} m^{-1})	0.24	0.27
W_{tot}	**-0.97 (0.92)**	**0.009**	(J kg^{-1} m^{-1})	0.48	0.53
Recovery	**0.97 (0.78)**	**0.004**	(%)	69.5	62.7
C_{net}	**1.78 (1.58)**	**0.006**	(J kg^{-1} m^{-1})	2.29	1.87
Efficiency	**-0.97 (0.65)**	**0.001**	(%)	21.4	28.0

Abbreviations: OA: osteoarthritis; W_{ext}: external mechanical work; Wv: work done against gravity; CoM: centre of mass; W_{int}: internal mechanical work; W_{tot}: total mechanical work; C_{net}: mass-specific net cost of transport.

Bold values are significant with $P < 0.05$.

[a]N=10 subjects with ankle OA for mechanical work and energetics variables, N=17 OA ankles (3 normal ankles were excluded) for spatiotemporal, kinematics and kinetics variables.

[b]Z-score is expressed as mean (standard deviation) (one sample t-test) or median [P25 ; P75] (one sample Wilcoxon signed-rank test).

[c]p-value indicates if the Z-score significantly differ from the normal population mean = 0.

[d]Absolute values means for each gait variables are strictly indicative as these values represent the mean of raw data of patients/controls that have walked

Relationship between ankle function and mechanical and metabolic variables

When normalized to walking speed, a significant negative correlation was found between ankle power and C_{net} (r_s=-0.62; P=0.048) (Table 2), meaning that the less ankle power was generated during stride, the more metabolic energy was consumed. In contrast, a positive correlation was found between ankle power and muscular efficiency (r_s=0.71; P=0.019), indicating that the more the ankle function was affected, the more the efficiency of walking was impaired.

Table 2. correlations between ankle power and mechanics/energetics for the ankle osteoarthritis group

		W_{tot}[a]	C_{net}[a]	Efficiency[a]
Ankle Power[a]	r_s	0.47	**-0.62**	**0.71**
	P-value	*0.160*	*0.048*	*0.019*

Abbreviations: r_s: Spearman rank order correlation; W_{tot}: total mechanical work; C_{net}: mass-specific net cost of transport

Bold values are significant with P<0.05.

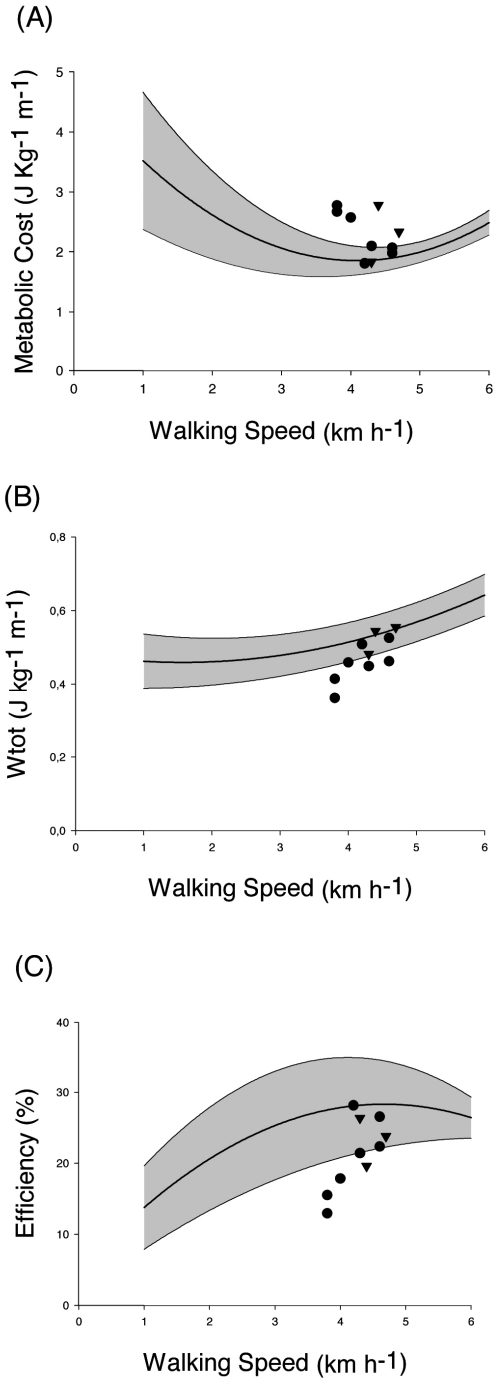

Fig. 3. Metabolic cost (A), total mechanical work (W_{tot}) (B), and efficiency (C) as function of walking speed for patients with unilateral (green triangle symbols) and bilateral (red circle symbols) ankle OA. The gray area represents normal values (mean ± 1 SD) of the control group walking at different speed between 1 and 6 km h^{-1}

Discussion

The aim of our study was to assess the impact of ankle OA on the energetics and mechanics of gait, while taking into account the slower speed generally adopted by our patients [5;6]. Speed-normalization showed that ankle OA had a moderate, though significant impact on the energetics and mechanics of gait. Metabolic cost increased, while mechanical work decreased. As a consequence, muscular efficiency also decreased. These changes were associated with a surprising efficacy of the pendulum mechanism. Significant alterations in ankle kinematics and kinetics were found in ankle OA patients as well as significant knee and hip alterations.

Kinematics and kinetics

A significant reduction in the active dorsi- and plantarflexion during push-off was observed in the ankle OA group, probably being due to several factors, including antalgic response and bony deformity. Reduced hindfoot motion in the sagittal plane was previously reported to be the greatest change in end-stage ankle OA [5;6]. In terms of kinetics, the peak plantarflexion moment at push-off increased (Table 1), which is contrary to the study of Valderrabano *et al.*[6].

Peak ankle power was lower in the OA group due to the decrease in angular velocity caused by the reduced ankle ROM. Limited push-off meant that some additional work may have been required from other joints, perhaps at other moments during the stride. However, the lower limbs revealed a different movement pattern, with a lower peak flexion moment and positive hip flexor power during early swing phase, lower peak knee extensor moment during the loading response, and lower peak eccentric knee extensor power during the swing phase.

Metabolic cost

For patients with unilateral impairment of ankle function due to end-stage OA [10], following TAA [10;12], or arthrodesis [11;13], greater metabolic expenditures were reported compared to normal walking subjects, as evidenced by an 8-28 % increase in C_{net}. Our study confirmed this increase inC_{net} (+22%) (Fig. 3A), revealing it to be negatively correlated with ankle power during push-off. The ankle joint, especially the third foot rocker, plays a major role in decreasing the vertical displacement of the CoM, which in turn decreases energy consumption in normal and pathological gaits [15;26]. Therefore, the increased energy cost in ankle OA patients may partly be due to the increase in their vertical CoM displacement

resulting from a decrease in the third rocker [26;27]. Indeed, in pathological gait, the increase in energy cost has been attributed to several factors, such as increased muscle mechanical work [28;29], increased vertical displacement of the CoM [26;29], and altered efficiency of pendulum-like mechanism of gait [8;11;12;30].

Mechanical work

In comparison to the control group, our OA patients showed a 10% reduction in total mechanical work (Fig. 3B), which did not explain the increase in C_{net}. The decrease in W_{tot} was due to the reduction of its two components, W_{int} and W_{ext}, although the decrease in W_{ext} was not significant (P=0.085). A moderate reduction in W_{int} could be anticipated from a decrease in ROM at ankle and hip level, and subsequent decrease in angular speed. In contrast, an increase in W_{ext} was expected to result from the excessive vertical displacement of the CoM.The absence of excessive W_{ext} could be explained by an improved efficacy of the locomotor mechanism. Recovery was a measure of the amount of muscular work undertaken during the pendulum exchange between potential and kinetic energy, reaching a maximum of 60-65% during normal gait at optimal speed [24]. In our study, the ankle OA patients attained 69.5% of recovery on average, representing a mean of Z=0.97. We hypothesized that walking with ankle OA may, in some way, increase the transfer of kinetic and potential energy. During walking, recovery reaches a maximum at an intermediate speed when the difference in amplitude of the potential and kinetic energy curves approaches zero and the phase difference between the potential and kinetic energy curves approaches 180° [31]. To move the CoM, the locomotory muscles must provide the work necessary to overcome the losses occurring during the transfer of potential and kinetic energies. An increased recovery index as observed in the ankle OA group could be therefore explained by (1) the relative amplitude of the potential and kinetic energy curves, (2) their shape and (3) their relative phase [32]. More information about the pendular mechanism of walking may be obtained by analyzing how the pendular transduction of the mechanical energy occurs during the step cycle (instant recovery) [32]. Although further investigations are needed, one could hypothesize that patients with ankle OA increased their recovery because of the presence of higher amplitude of potential energy due to an increased vertical CoM displacement or a better phase difference between potential and kinetic energies. A similar effective mechanical system with enhanced recovery was previously reported in various orthopedic and neurological disorders [30;33]. Our results are in accordance with previous studies, showing that the pendulum mechanism is still intact. The pendulum mechanism may be a strategy to help preserve a reasonable amount of the muscle work and save energy despite significant joint impairments.

Muscular efficiency

As a result of the decrease in W_{tot} and increase in C_{net}, muscular efficiency was reduced (Fig. 3C). In normal gait, efficiency reaches a maximum of 30-35% at 4.5 km h^{-1}[21;24]. In our study, efficiency showed a 24% decrease in ankle OA patients compared to control group. The decrease in muscular efficiency significantly correlated with lower ankle power, suggesting that the energy waste may have been directly related to the affected muscle efficiency around the joint.

Hypotheses to explain the increase in C_{net}

As muscle work did not increase, the higher energy cost may be explained by the decrease in muscle efficiency. However, the decrease in muscle work may be the result of methodological limitations in calculating mechanical muscle work [12]. According to the double-inverted pendulum model of walking [34;35], relevant muscle work is required to redirect the CoM from one circular arc to the next during the step-to-step transition [35]. When both feet are on the ground, both legs simultaneously exert horizontal forces in opposite directions in order to redirect the CoM trajectory; the back leg performs the positive push-off work, while the front leg performs the negative collision work [34]. The mechanical work of one leg pushing against the other during the double contact phase ($W_{int,dc}$) was ignored in the way we calculated W_{int} and W_{ext}[36;37]. However, at optimal walking speed, $W_{int,dc}$ represents a substantial part of the energy cost of walking [35]. In patients following TAA, Doets *et al.*[12] reported that mechanical energy dissipation during step-to-step transition significantly correlated with an increase in C_{net}. Consequently, $W_{int,dc}$ may markedly be increased in ankle OA patients, leading to an underestimation of the mechanical work. In order to measure $W_{int,dc}$, subjects would need to walk on separate force platforms under each leg such as on a split-belt treadmill.

Other factors likely affect the energy cost of walking. An important contributing factor may be the energy related to balance control [38]. It is possible that patients with ankle OA present an impaired balance control capacity. Compensations in order to increase the dynamic stability and reduce the between-step variability of gait pattern may elicit a substantial and meaningful metabolic energy demand [38;39]. Stiffening the body through co-contractions could be one of these strategies. In an attempt to stabilize gait, increased EMG activity timing and co-contractions of the lower leg muscles were found in walking after TAA and in patients with ankle OA prior TAA intervention [40]. Frictional losses that mainly occur within antagonistic muscles doing work on each other as measured during co-contractions, would decrease the efficiency by using metabolic energy with no apparent work produced [41].

The kinematic model used in this study [20] considered the foot as a single rigid body. This is clearly a simplistic model because only the movements of the tibiotalar joint are estimated. Motions of the joints of the foot and ankle are complex and difficult to quantify unless considering the foot as three functional segments (rear-, mid- and forefoot) by using more sophisticated foot models [42]. Although the larger foot movements of the tibiotalar joint (*i.e.,* foot's third rocker) are correctly estimated by the Davis model, further investigations are required on this point as some motion limitations may well be mid-foot, particularly in ankle osteoarthritis. However, we can reasonably hypothesize that the small movements involved at the mid- and fore foot level would have little influence on the global mechanical and energetic variables we measured to assess gait.

Conclusions

To our knowledge, this is the first study that quantitatively describes the energetic and mechanical changes during gait as a result of unilateral and bilateral ankle OA allowing for the calculation of gait efficiency. This information provides a quantitative baseline enabling us to better understand the dynamics of this condition and accurately measure disease progression. Based on the results of our study, the conclusion can be drawn that metabolic energy cost is higher in ankle OA patients, due to a significant decrease in muscle efficiency, the modifications being proportional to the impaired ankle function. Furthermore, patients with ankle OA are able to adopt a walking strategy which improves energy recovery through pendulum mechanism. This is likely to be a compensatory mechanism so as to economize energy which would counterbalance the energy waste due to a low muscle efficiency.

Acknowledgements

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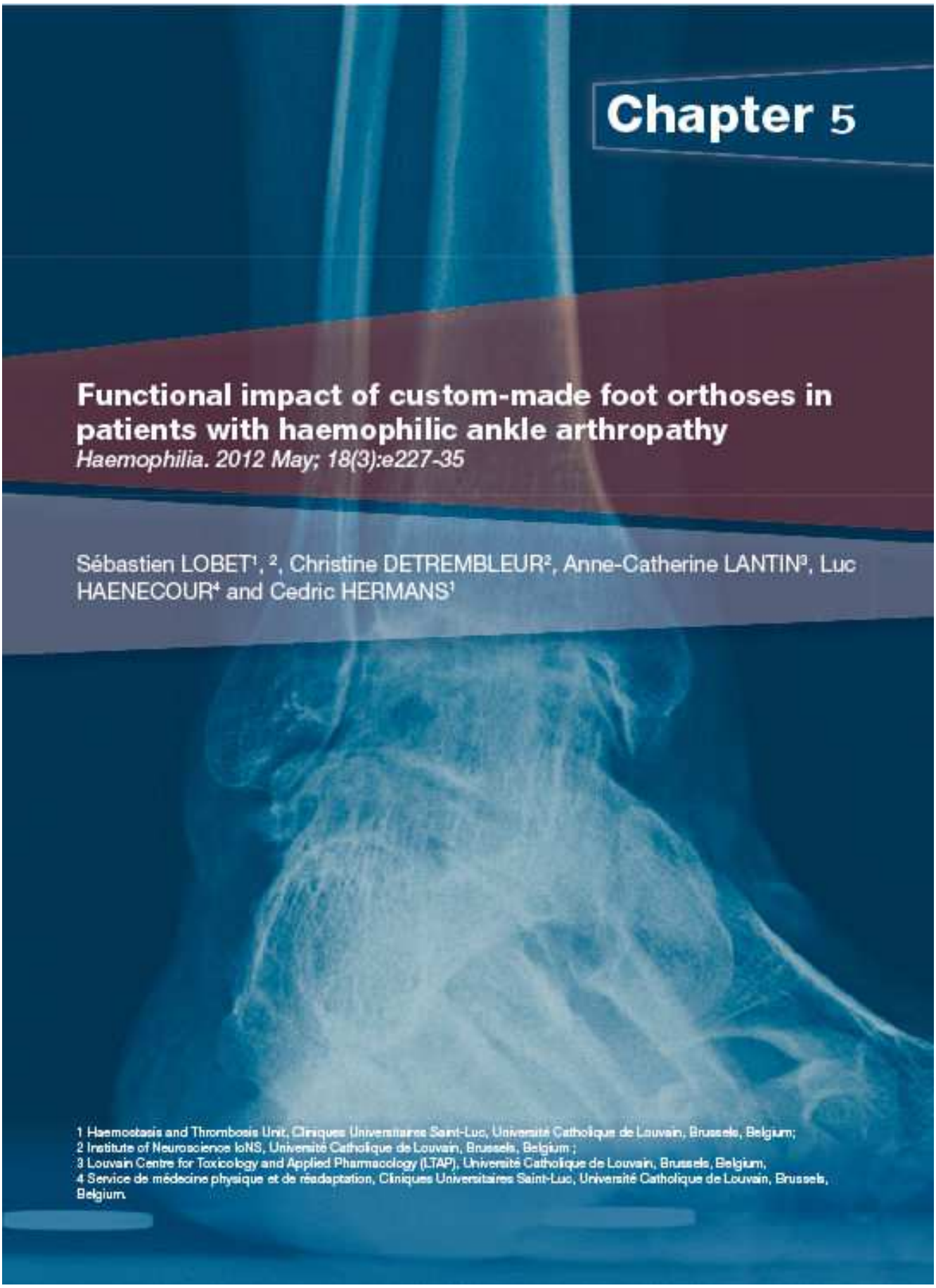

Chapter 5

Functional impact of custom-made foot orthoses in patients with haemophilic ankle arthropathy

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Summary

Although foot orthoses are often prescribed to patients with haemophilia (PWH) and ankle arthropathy, the efficacy and biomechanical effects of such devices are not fully understood. We experimentally investigated the effects of orthopedic insoles (OI) and shoes (OS) in PWH presenting ankle arthropathy, with specific attention being paid to pain, spatiotemporal parameters, kinematics and kinetics of lower limb joints, as well mechanical and energetic variables. Using three-dimensional gait analysis (3DGA), synchronous kinematics, kinetics, spatiotemporal, mechanics, and metabolic gait parameters were measured in 16 PWH with ankle arthropathy. The revised Foot Function Index (FFI-R) and 3DGA were determined in patients wearing neutral running shoes at two time points (T0 and T1), with OI (*n*=11) or OS (*n*=5) being subsequently prescribed. Patients, while wearing their orthoses, were re-evaluated using 3DGA, FFI-R, and satisfaction questionnaires (T2). OI and OS provided significant pain relief and comfort improvement in more than half of the patients, with minimal side effects. OI had limited impact on gait pattern, whereas OS significantly improved the propulsive function of the ankle. Biomechanical changes induced by OI and OS were independent of their ability to improve comfort, while being insufficient to influence knee and hip kinematics and kinetics, or mechanical and energetic variables. These findings suggest that OI and OS may have beneficial effects on ankle joints in PWH. Self-reported clinical tools such as FFI-R and satisfaction questionnaires are sufficiently sensitive for assessing the efficacy of foot orthoses in PWH.

Introduction

The ankle is a common site for spontaneous bleeding in patients with haemophilia (PWH). Recurrent haemarthroses may progressively damage the cartilage, bone, and soft tissues, resulting in irreversible chronic arthropathy [1;2]. Foot deformities are common in patients with haemophilic ankle arthropathy, including valgus/varus malalignment of the hindfoot and flat/cavus foot, due to growth disturbance of the distal tibia, talar deformity, and subtalar involvement [1-3]. These deformities may become irreversible in the long term without appropriate treatment [2], and patients with foot deformities often experience discomfort while walking or standing for long periods [4].

Many conservative therapeutic treatment modalities have been described in PWH with ankle arthropathy, including foot orthoses [2;5;6]. Orthopedic insoles (OI) and shoes (OS) are designed to prevent or correct deformities as well as improve foot comfort by spreading pressure, unburden painful areas, absorb shock, and reduce joint loading [6;7]. They aim to control the amount, rate, and temporal sequence of subtalar joint movements [7].

Orthopedic insoles are defined as contoured, removable in-shoe devices that are moulded from an impression of the foot [8]. They are made from different soft compressible or semi-rigid materials and incorporate several corrections, including medial or lateral supports, which provide additional stability under the longitudinal arch and metatarsal area (Fig. 1a and 1b). OS are moulded shoes (Fig. 1c and 1d) that stabilise the foot while standing or walking, and display shock-absorbing properties that transfer weight-bearing stresses, with a sole form that facilitates the rolling movement of the step [5]. Contrary to OI that promote sagittal plane motion, OS restrict the ankle movements.

Although the effectiveness of foot orthoses has been demonstrated in rheumatoid arthritis (RA) [9-13], it is still unclear whether this can be extrapolated to PWH. In a few studies, OI were shown to reduce ankle pain and bleeding [14;15], while improving stability in PWH [16].

The biomechanical impact of OI and OS is not fully understood, as published reports mainly focused on the effects of orthoses at the foot level rather than on the lower limbs and global gait pattern. To address these limitations, we experimentally investigated the effects of OI and OS in PWH presenting ankle arthropathy, with specific attention given to pain and gait variables.

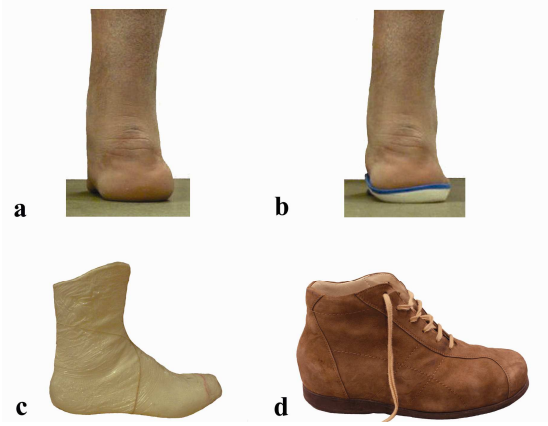

Fig.1. Orthopedic insoles were proposed as first-intention option to patients with partially correctable rear-foot pronation (Fig. 1a and 1b). Orthopedic shoes were molded on the patient's foot (Fig. 1c) under semi weight-bearing conditions, being made of a double layer of leather (Fig. 1d).

Material and methods

Subjects

Sixteen male patients diagnosed with haemophilia-related bilateral ankle arthropathy were followed up between March 2008 and December 2010, at the Haemophilia comprehensive centre of the Cliniques Universitaires Saint-Luc, Brussels, Belgium. Their characteristics are presented in Table 1. Of these, 13 patients had severe (one-stage FVIII or IX assay <1 IU/dl) and three moderate haemophilia (one-stage FVIII or IX assay between 2-5 IU/dl), with 15 patients suffering from haemophilia A and one from haemophilia B.All patients were capable of independent gait, without needing assistance. Exclusion criteria included prior use of OI and OS and co-morbidities with an impact on walking, such as neurological and cardiopulmonary diseases. The median Pettersson radiological score [17] of the ankle was 8 (P25: 7; P75: 9). The study was approved by the institutional ethics committee, and all participants provided informed consent.

Table 1. Characteristics of the study group (n=16)

Age (years)	41 ± 11 (21-60)
Weight (kg)	81 ± 15 (63-123)
Height (m)	1.77 ± 0.06 (1.67–1.87)
BMI (kg/m^2)	26 ± 4 (21-39)
Haemophilia A/B	(15/1)
Factor deficiency (severe/moderate/mild)	(13/3/0)
Medical treatment	
Prophylaxis/on-demand treatment	(7/9)
Ankle assessment (n=16 X 2)	
Ankle arthropathy (unilateral/bilateral)	32 (0/16)
Pettersson radiological score (max. 13)	8 [7;9]
Associated lower limb arthropathy	
Knee arthropathy (unilateral/bilateral)	(5/1)
Total knee replacement (unilateral/bilateral)	(4/3)
Total hip replacement (unilateral/bilateral)	(1/0)

Values are mean ± SD (range) or median [P25;P75].
BMI, body mass index

Protocol

Patients wearing neutral running shoes (Kalenji success Decathlon®, Villeneuve d'Ascq, France) were assessed using three-dimension gait analysis (3DGA) at baseline (T0) and after a mean follow-up of 17±5 weeks (T1). Subjects were required to complete the region-specific Foot Function Index-Revised short-form (FFI-R). The FFI-R is the revised version [18] of an anatomically-specific outcomes instrument with established validity, test-retest reliability, internal consistency, and responsiveness [18-21]. The FFI-R assesses self-reported foot function in terms of the following aspects: pain (*e.g.* "During the past week, how severe was your foot pain when you first stood without shoes"), stiffness (*e.g.* "During the past week, how severe was your foot stiffness before you get up in the morning"), difficulty (*e.g.* "how much difficulty did your foot problems cause you climbing stairs"), activity limitation (*e.g.* "how much of the time did you limit your outdoor activities because of foot problem") and psychosocial issues (*e.g.* "how much of the time did you feel awful because of foot problem"). The maximum possible score is 100, indicating maximum alteration. Psychometric properties of the FFI-R have been tested using Rasch analysis established on a sample of 92 patients, of whom 69% (63/92) reported having degenerative arthritis [18]. Given its robust psychometric properties and sensitivity in PWH [14;22], the FFI-R was selected to assess the subjects in this study.

Following T1, patients were referred to a multidisciplinary podiatry clinic consultation. Eleven patients were prescribed OI and five OS, with the delivery time being 3 weeks for OI and 6-8 weeks for OS. After 40±18 weeks (T2), 3DGA was performed, with the subjects wearing their OS or OI fitted inside the neutral running shoes. As some foot orthoses required some modification before the patient felt comfortable, this partially accounted for the longer time period between T1 and T2 than between T0 and T1. Subjects were asked to complete a third FFI-R questionnaire, in addition to a satisfaction questionnaire based on the MOS questionnaire [23], to assess the orthose impact over the T1-T2 period.

Prior to 3DGA assessment, patients had not experienced acute joint or muscle bleeding during the previous 30 days. Subjects who occasionally used anti-inflammatory drugs (NSAID) were instructed to stop taking them for at least 72h, whereas daily NSAID users were told not to interrupt the treatment.

Foot orthoses

All orthoses were manufactured by the same laboratory. OI were fabricated from a plaster model of the patient's foot taken from a foam box impression. While most OI were made using sheets of high-density polyethylene foam over the casts (Fig. 1b), two patients

received leather-lined cork OI. For metatarsal relief, extra-density padding was incorporated into the OI proximally to the metatarsal to improve longitudinal arch weight-bearing.

OS manufacturing necessitated a custom molding of the patient's foot (Fig. 1c) under semi-weight-bearing conditions. The insoles of the shoes were made from two different podofoam® XA 1000 and XA 600 layers (Podofrance, Noisy-le-grand, France), with a temporary shoe in thermoformable polymer being made using a vacuum process on the pre-existing mould. The definitive shoe (Fig. 1d) was composed of a double leather layer, while the sole was made of soft rubber with a rocker shape to facilitate the rolling of the step. Features such as shoe depth and model, heel height, sole stiffness, and fastening apparatus (laces, Velcro, or buckle) were taken into consideration.

Gait analysis

The basic principles of 3DGA are summarised as follows, although a description of its technical aspects may be found in two previous publications [24;25].

In short, 3DGA involved synchronous spatiotemporal, kinematic, kinetics, mechanics, and metabolic measurements. Walking trials were conducted while the patients walked at a self-selected speed on a treadmill that was mounted on 3D strain-gauge force transducers (Fig. 2), and for each subject, the same speed was imposed at T0, T1, and T2. Segmental kinematics was measured with six infrared cameras, which recorded the 3D coordinates of reflective markers positioned on specific anatomical landmarks and then computed angular displacements. A force platform located under the treadmill simultaneously measured the ground reaction forces generated by the body in three directions. The net moments of force and power that were generated or absorbed at the major lower limb joint muscles in the sagittal plane were estimated, with spatiotemporal parameters being assessed using 3D position data. The internal work (W_{int}), *i.e.,* positive work performed by the muscles to move the limbs in relation with the body's centre of mass (CoM), was calculated based on kinematics data [26]. The external work (W_{ext}), *i.e.,* work performed to lift and accelerate the centre of mass in relation to the surroundings, was computed [26], the total work (W_{tot}) being defined as the sum of W_{ext} and W_{int}. 'Recovery' was quantified as the percentage of mechanical energy saved via a pendulum-like exchange between gravitational potential energy and kinetic energy of the CoM [26].

The oxygen consumption rate was measured using an ergospirometer. The mass-specific net cost of transport (C_{net}) was calculated by dividing net energy consumption by walking speed. The efficiency of positive work production by the muscles during walking was calculated as the ratio of W_{tot} to C_{net}[27].

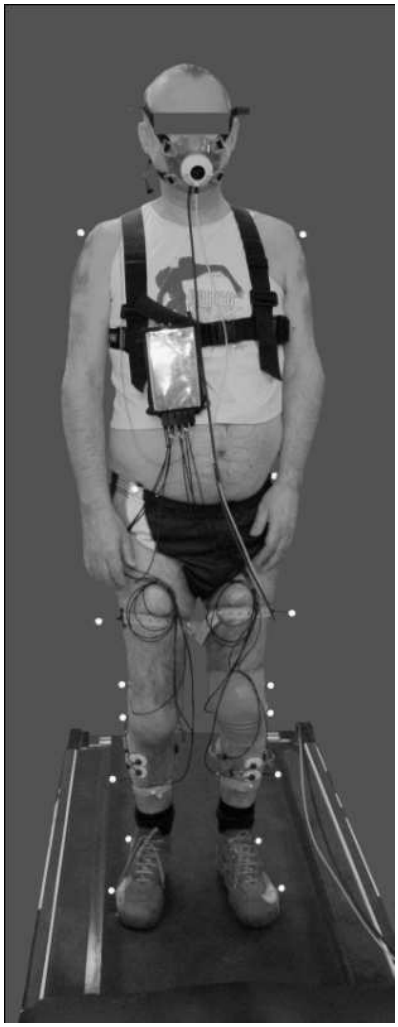

Fig.2. Three-dimensional gait analysis. The subjects walked on a custom-built motorized treadmill mounted on four 3D strain-gauge force transducers, while infra-red light sources around each camera reflected the retroreflective markers and generated reconstructed 3D trajectories.

Statistical analyses

Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA, 2002-2008). As subjects were measured repeatedly over time, a mixed model for repeated measures data with a compound symmetry covariance pattern was used for each outcome variable, which took into account the correlation between observations relating to the same patient [28]. The outcome variable at the first time point (T0) was used as a continuous baseline variable and the time variable (T1 and T2, pre- and post- treatment) as a binary variable. The mixed model was adjusted for two binary covariates: treatment (OS *vs.* OI) and satisfaction (satisfied *vs.* non-satisfied), with interactions between time and treatment, and time and satisfaction also being taken into account. Regression residuals were visually examined by ACL and SL for linearity of the model, and for independence, homoscedasticity, and normality of the errors.

Results

Satisfaction questionnaire

In total, 10 patients (63%) were satisfied with their foot orthoses, all of them reporting a substantial reduction in pain, with four noting improved proprioception (Table 2). Three patients reported a substantial reduction in pain killer/NSAID consumption, three exhibited a subjectively improved walking endurance, and one observed a decrease in swelling towards the end of the day. Four patients (25%) did not show any improvement while wearing the orthosis, but they did not report any adverse effects. Two patients abandoned the orthoses because of increased ankle pain due to Achilles tendonitis (diagnosed by clinical examination).

Table 2. Results of the satisfaction questionnaire and adverse effects of custom-made foot orthoses

Questions	Number of patients (%)
Total responses to satisfaction questionnaire	16 (100)
Are you satisfied with the comfort of your orthoses?	
Yes, improvement	10 (63)
No change	4 (25)
No, deterioration	2 (13)
What are the advantages of your orthoses?	
Pain reduction	10 (63)
Improved proprioception	4 (25)
Diminution of pain killer/NSAID	3 (19)
Improved walking endurance	3 (19)
Decrease of swelling	1 (6)
What are the disadvantages of your orthoses?	
Tendonitis	2 (13)

NSAID, non-steroidal anti-inflammatory drug.

Mixed models

Orthoses impact regardless of the OI or OS type. Overall, the mechanical and energetic variables were not influenced by the orthoses, except for the 'recovery' index, which was significantly increased by 2.2% (P=0.037). Regarding kinematic and kinetic variables, wearing orthoses was associated with a 3.1° decrease in external rotation of the foot progression (angle between the long axis of the foot and the direction of travel as seen from above) (19.7° *vs.* 16.6°, P<0.001) (Fig. 3l), in addition to a 2.0° increase in knee flexion amplitude during stance phase (9.9° *vs.* 11.9°, P<0.001) (Fig. 3f) and 0.32 W kg^{-1} increase in peak concentric power during push-off phase (1.86 *vs.* 2.18 W kg^{-1}, P= 0.004) (Fig. 4f).

Impact of orthoses, with the distinction between OI and OS. For several gait variables, the mixed model was able to highlight differences between OI and OS. OI had no influence on gait variables other than that reported when not distinguishing between OI and OS types, whereas OS had a significant influence on spatiotemporal parameters, kinematics, and kinetics. Using OS led to a decrease in cadence of 4.5 step min^{-1} (110.0 *vs.* 105.5 step min^{-1}, $P<0.001$) and was associated with a 2-cm increase in step length (0.66 *vs.* 0.68 m, p = 0.012) (Table 3), while stance phase duration remained unchanged. Total hip ROM and knee ROM in swing phase measured by 3DGA increased by 3.1° (40.4° *vs.* 43.5°, $P=0.011$) and 4.4 ° (54.3° *vs.* 58.7°, p <0.001), respectively (Fig. 3a and 3d). Peak plantar flexion moment of the ankle increased by 0.30 N m kg^{-1} (0.85 *vs.* 1.15 N m kg^{-1}, $P<0.001$) (Fig. 4a).

Impact of orthoses, when distinguishing between satisfied and non-satisfied patients. Total FFI-R score was found to significantly decrease by nine points in patients who reported being satisfied with the orthoses (33 *vs.* 24 points, $P = 0.007$), but no significant change was observed in those being non-satisfied (Fig. 5). This improved total FFI-R score may largely be accounted for by a 13-points decrease in the “pain” subscale among satisfied patients (30 *vs.* 17 points, $P=0.006$).

Aside from the significantly decreased cadence of 3.6 step min^{-1} (108.3 *vs.* 104.7 step min^{-1}, $P<0.001$) that was reported only in satisfied patients, the biomechanical impact of the orthoses was similar between satisfied and non-satisfied patients.

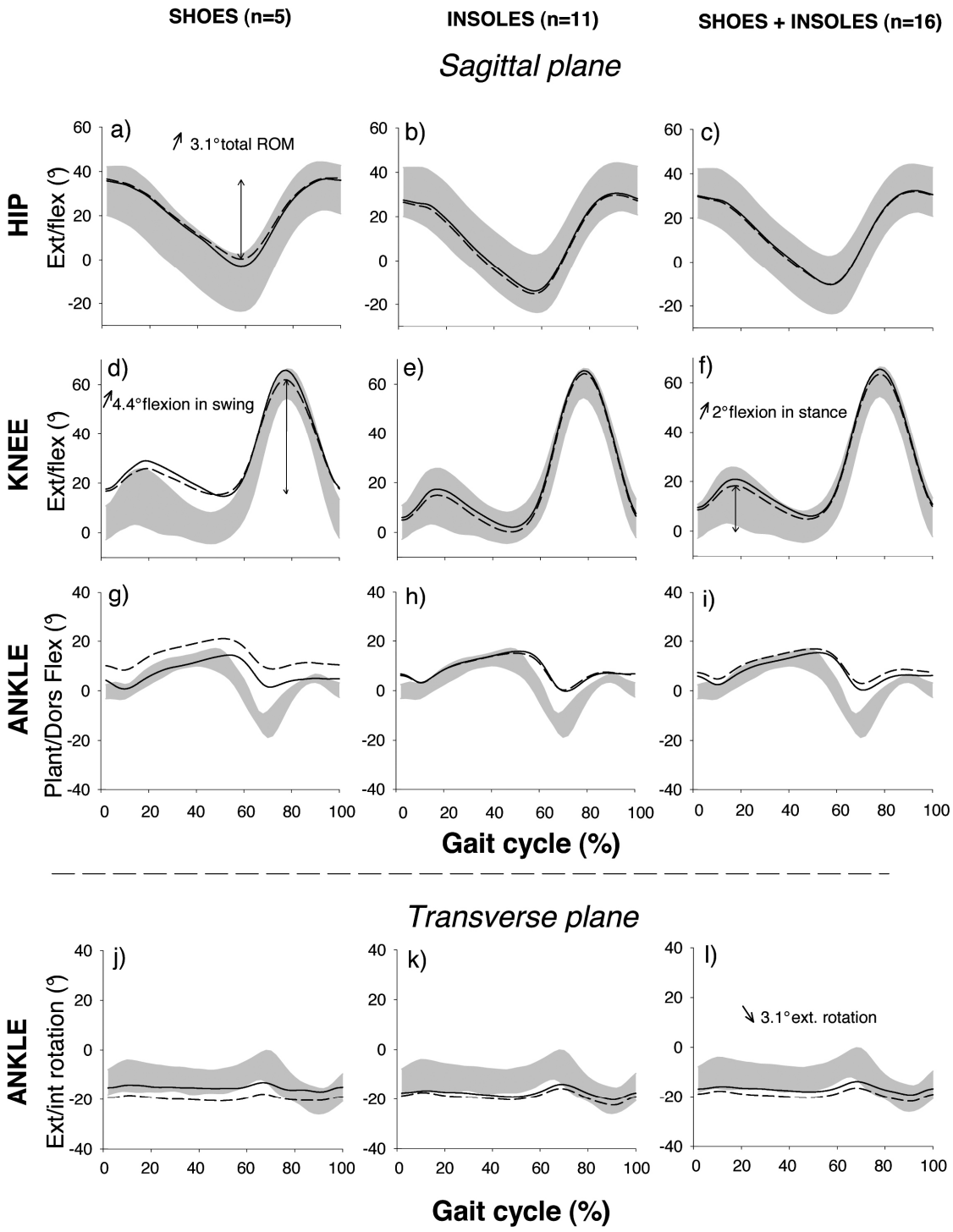

Fig.3. Mean kinematic data of hip, knee, and ankle, with (black line) and without orthoses (dotted line), as a function of the percentage of a walking stride. The grey area represents mean ± 1 standard deviation of a normal gait at 1.11 m s^{-1}.

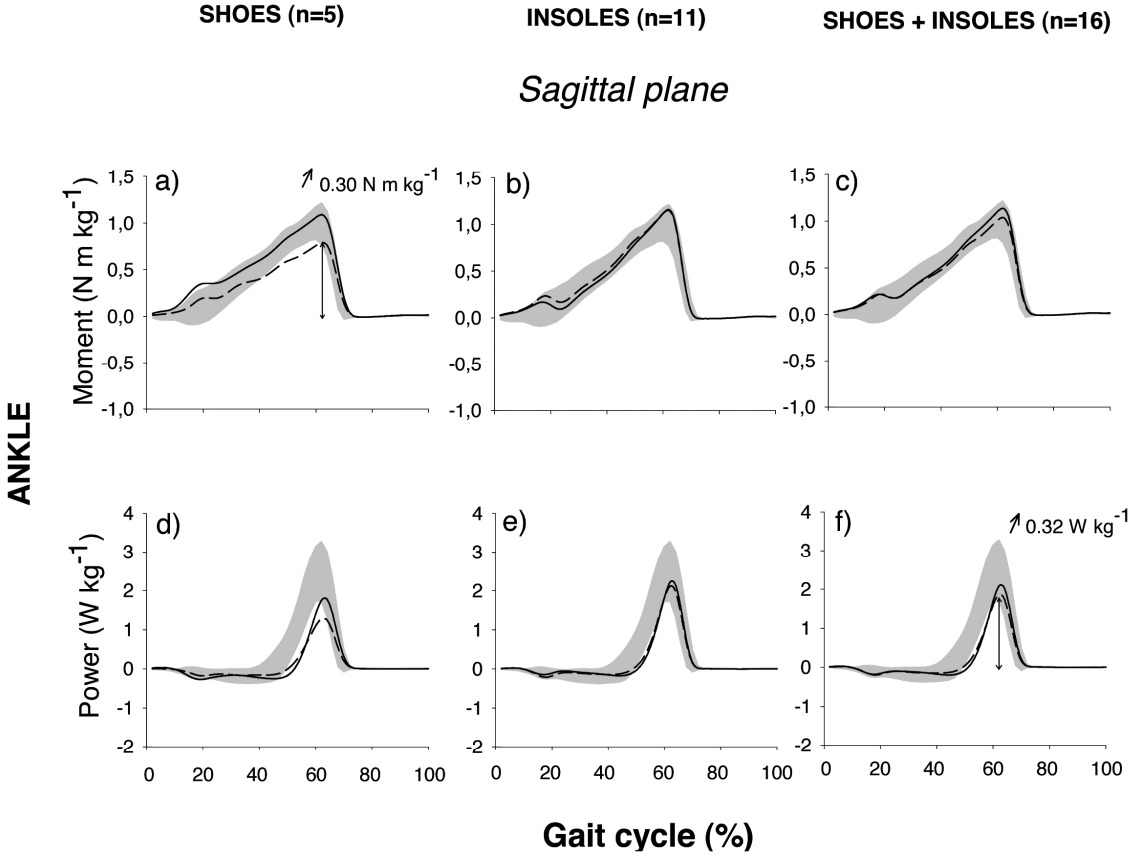

Fig.4. Mean kinetic data of the ankle, with (black line) and without orthoses (dotted line), as a function of the percentage of a walking stride. The grey area represents mean ± 1 standard deviation of a normal gait at 1.11 m s^{-1}.

Table 3. Mean spatiotemporal, mechanic and energetic variables results for the Orthopedic Shoes and Insoles groups in the pre- and post-orthosis intervention conditions. As comparison, normal values established in healthy subjects are also showed.

	Orthopaedic Shoes (n=5)[b]		Orthopaedic Insoles (n=11)[b]		
	Pre	Post	Pre	Post	Normal Values[a]
Spatiotemporal parameters (n=32 limbs)					
cadence (step min^{-1})	110.0 ± 5.7	105.5 ± 9.7*	105.6 ± 7.9	105.7 ± 7.2	105.9 ± 6.1
step length (m)	0.66 ± 0.09	0.68 ± 0.08*	0.69 ± 0.08	0. 69 ± 0.07	0.72 ± 0.05
stance phase duration (% gait cycle)	65.6 ± 2.2	66.1 ± 1.9	65.7 ± 1.2	65.8 ± 1.2	64.8 ± 1.2
Mechanical work / Energetics (n=16 subjects)					
External work (J kg^{-1} m^{-1})	0.236 ± 0.044	0.261 ± 0.064	0.253 ± 0.039	0.252 ± 0.028	0.252 ± 0.042
Internal work (J kg^{-1} m^{-1})	0.255 ± 0.026	0.265 ± 0.043	0.238 ± 0.067	0.247 ± 0.100	0.260 ± 0.034
Total work (J kg^{-1} m^{-1})	0.493 ± 0.056	0.528 ± 0.097	0.489 ± 0.072	0.497 ± 0.104	0.510 ± 0.061
Recovery (%)	64.0 ± 9.0	65.1 ± 9.2*[$]	63.0 ± 8.4	66.3 ± 5.3*[$]	62.6 ± 7.2
Cost (J kg^{-1} m^{-1})	2.80 ± 0.91	2.91 ± 1.03	2.47 ± 0.67	2.46 ± 0.47	1.85 ± 0.27
Efficiency (%)	18.5 ± 7.1	18.7 ± 6.5	21.4 ± 5.9	21.2 ± 6.3	28.3 ± 6.7

Values are mean ± SD.

*Significant change (P <0.05) as regard to the pre-orthose condition.

[a]Normal values at 1.11 m s^{-1} established in eight healthy subjects (mean age 29 ± 16 years; weight 65 ± 10 kg; height 1.74 ± 0.05 m), with no history of orthopedic or neurological pathology affecting the lower limbs.

[b]Means, but not SDs, are adjusted for covariates introduced in the mixed models (see Material and Methods).

[$]Change in this variable was significant when both orthopedic shoes and insoles groups were considered together.

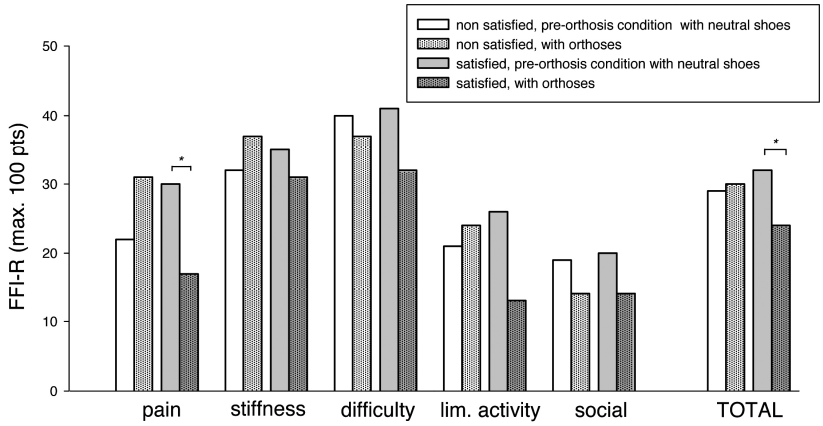

Fig. 5. Results of the Foot Function Index-Revised form (FFI-R) when using neutral shoes or orthoses for satisfied (n=10) and non-satisfied (n=6) patients. * Statistically significant differences.

Discussion

Foot orthoses are widely prescribed for patients with RA[9-13], midfoot OA [29], or plantar heel pain [30], but few studies evaluate their effects in PWH. Our study was designed to evaluate the impact of OI and OS on gait parameters, patient satisfaction, and functional improvement in PWH with foot involvement.

Impact of orthoses on self-reported satisfaction and function

The use of orthoses was reported to be satisfactory by more than half of the patients, resulting in a significant reduction in the pain subscale score and total FFI-R score (Fig. 5). South *et al.*[15] observed that combined physiotherapy and podiatry resulted in excellent patient satisfaction scores and significant pain reduction. Slattery and Tinley [14] also reported a significant pain reduction in 16 PWH using OI over a 6-week period without rehabilitation.

Currently, there is no clear understanding of how foot orthoses affect foot pain and improve comfort. Several theoretical explanations have been proposed, notably that orthoses resist or facilitate the motion of arthritic joints [29], reduce plantar fascia strain by minimising arch deformation[31], decrease joint loading by acting as a cushioning interface between the ground and foot [32], or alter proprioception involved in muscle activity regulation [33;34]. Given that high (pes cavus) and flat-arched (pes planus) foot types are common in PWH, these deformities may result in increased load and pressure on the foot structure, which are then transferred to proximal joints, such as the knees, hips, and lower back [35]. Foot orthoses may also be instrumental in reducing plantar pressure [9;13;30].

Unlike the choice of material that appears unable to reduce peak pressures, OI conformity seems to depend most importantly on the design component for reducing heel plantar pressure [36]. These observations support our belief that in the setting of a podiatry clinic, a tailored orthopedic approach using custom-made foot orthoses is likely to be more efficient for PWH than prefabricated orthoses.

Impact of orthoses on gait pattern

The use orthoses was associated with a decreased external rotation of the foot progression (Fig. 3l). The foot progression angle may provide some indication as to the torsional abnormality of the foot and whole limb. A reduction of the angle may be due to the correction of excessive rear-foot pronation combined with fore-foot abduction as a result of using OI or OS, which is in line with most published studies evaluating the effects of OI on rear-foot alignment in the frontal plane [7;37-39].

Orthopedic insoles had no impact on ankle kinematics and kinetics. Although significant, the changes associated with OS in hip and knee kinematics (Fig. 3a and 3d) were probably not clinically important. On the contrary, OS improved the propulsion of the ankle (Fig. 4a and 4d). At the push-off phase, the peak ankle moment improved with OS (Fig. 4a), whereas peak ankle power improved significantly only when OS and OI data was considered together (Fig. 4f). This was likely due to low statistical power, given the small number of patients (n=5) treated with OS. As ankle ROM at the push-off phase did not improve with OS, the increased ankle power was likely attributed to increased moments. As the lever arm remained unchanged between neutral shoes (T1) and OS conditions (T2), increased joint moment could only be attributed to increased forces that developed at the ankle level. Increases in ankle moment and knee flexion in the stance phase (Fig. 3d) suggest that patients with OS experience improved weight acceptance, probably due to improved comfort and reduced ankle pain. These results are in contradiction with those of Chen *et al.*[4] who reported that the peak ankle plantar-flexion moment tended to be smaller in flat foot patients walking with OI.

Regarding spatiotemporal parameters, previous publications reported that foot orthoses increased the step length in RA patients [40]. In our study, OS was shown to increase step length, while decreasing cadence, which is thought to be related to increased total hip ROM (Fig. 3a) and improved propulsion phase of the ankle.

Otman *et al.* [41] reported an 8% decrease in oxygen consumption in flat feet patients when walking with OI. Furthermore, Kavlak *et al.* [40] showed that using OI for 3 months lowered energy expenditure during gait in RA patients. However, in our series, we did not detect any difference between pre- and post-orthoses conditions in terms of metabolic cost, mechanical work, and gait efficiency. The recovery index, a measure of the muscular work undertaken during the pendulum exchange between potential and kinetic energy, was the only mechanical variable, which improved slightly when using orthoses.

The principal limitation of this study was the sample size. Haemophilia is a rare disease and our exclusion criteria were very strict (*e.g.* prior use of OI and OS). It was therefore difficult to recruit more patients in the trial. As our sample was small, it should be

highlighted that the absence of significance could be due to the low statistical power. This also could explain that when a variable is applicable for both limbs independently (*e.g.*peak plantar flexion moment of the ankle), significant results could be separately observed in OS, as the presence of two limbs for each patient multiplied the sample size by two. On the contrary, when considering unique variables among the patients (*e.g.* recovery index), changes could only be observed when both OI and OS were considered together (*n*=16).

Indications, perspectives and side effects

There is no consensus with respect to the best type of foot orthoses for managing foot pain in PWH. Empirically, OI were proposed as the first option for patients with moderate ankle arthropathy or partially correctable rear-foot (Fig. 1a and 1b), whereas OS were prescribed to patients with more severe pain or poor ROM. With respect to gait kinematics, the rocker sole of OS provides several advantages, being thus used when there is only minimal motion at the forefoot joint or hindfoot joint [42;43]. It facilitates controlling joint motion by rocking the foot from heel strike through toe-off. Our statistical analysis revealed enhanced functional impairment (lower FFI-R score) and gait disturbances (increased metabolic cost, and decreased hip and knee ROM, and plantar flexion moment of the ankle) in OS patients compared with OI patients.

Given that our results show that foot orthoses are beneficial for some but not all PWH, it is important to understand which factors are associated with potential foot orthosis benefits, before drawing definitive conclusions on this modality. Previous studies reported significantly reduced ankle bleeding in PWH when using OI [14;15]. In contrast, Jorge Filho *et al.*[16] noted significantly increased traumatic bleedings when using OI over 6 months, owing to that fact that patients felt so safe when wearing OI that they indulged increasingly in activities likely to cause sprains and bleeding. Additionally, while this study provided useful insights into the immediate effects of OS and OI, long-term effects were not assessed. Therefore, further studies are required in order to determine the impact of foot orthoses on joint bleeding, along with their long-term effects.

In our series, two patients suffered from Achilles tendonitis due to OI. Although foot orthoses are considered to have minimal side effects, our two observed cases of Achilles tendonitis support the idea that correction in patients with a long history of foot deformation must be progressive.

Conclusion

Our study results suggest that foot orthoses may have beneficial effects on ankle joints in PWH. OI and OS provided significant pain relief and improved comfort in more than half of patients, with minimal side effects. While OI had a limited impact on gait pattern as evaluated using 3DGA, OS significantly improved ankle propulsion. The biomechanical changes caused by OI and OS were independent of their ability to improve comfort, as they were too limited to influence knee and hip kinematics and kinetics, or mechanical and energetic variables. Overall, 3DGA was not discriminative enough to determine the potential benefits of foot orthoses in PWH. Self-reported scales, such as FFI-R and satisfaction questionnaires, proved sufficiently sensitive to assess the efficacy of foot orthoses in PWH. Foot orthoses will likely make a substantial difference in terms of comfort and function for patients with limited access to replacement therapy.

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General Discussion and Perspectives

In patients with haemophilia (PWH), the long-term consequences of repeated haemarthrosis include joint cartilage damage and irreversible chronic arthropathy, resulting in severe impairments in locomotion. Quantifying the extent of joint damage is therefore of paramount importance in order to prevent disease progression and compare the efficacy of treatment strategies, such as prophylaxis.

According to the International Classification of Functioning, Disability, and Health (ICF) [1], musculoskeletal (MSK) impairments in PWH may stem from structural and functional abnormalities, which have traditionally been evaluated radiologically or clinically. Radiological scores are strictly focused on the structural aspects of impairment, whereas clinical scores address both the functional and structural features of impairment. However, clinical and radiological scores generally underestimate the degree of joint pathology in the early stages of arthropathy. In addition, they are insensitive to detect subtle changes in long term follow-up and unable to discriminate between different stages of arthropathy [2;3].

The aim of this thesis is to propose three-dimensional gait analysis (3DGA) as an innovative approach designed to focus exclusively on the functional component of the joint. Moreover, contrary to radiological and clinical examinations that usually assess the patient in supine position, *i.e.*, in a non-weight-bearing situation, 3DGA allows us to objectively quantify joint motion, muscle moment, and power under dynamic and weight-bearing conditions. This is of the utmost importance, as pain induced by weight-bearing activities most likely has a significant influence on the functional performance of the arthropathic joints.

This thesis aims to increase our knowledge about the biomechanical consequences of haemophilic arthropathy on gait pattern in PWH. In order to determine the scientific credibility of 3DGA, the psychometric properties of this tool were first tested. Thereafter, the impact of lower limb impairments on gait was studied in order to better understand the physiopathology of PWH gait. Finally, 3DGA was tested as an assessment tool in the context of a clinical study.This general discussion emphasizes the limitations and possibilities of the applied methods while highlighting directions for future research.

Psychometric characteristics of 3DGA

In **Chapter 1**, the correlations between structural alterations (determined by the most widely used haemophilia-specific radiological and clinical scores) and functional alterations (assessed by 3DGA and a validated self-reported ankle function assessment) were explored in terms of PWH with ankle arthropathy. Significant correlations were found between the self-reported functional assessment and three 3DGA variables representative of joint function, *i.e.*, ankle range of motion (ROM) in the sagittal plane, muscular moment, and power. These correlations proved that 3DGA appeared to measure what it really aimed to measure, namely the function of joints.

In the context of the ICF's "body structure and function" domain, we intended to clarify the relationship between the structural and functional assessments of a joint. Radiological and clinical scores were compared to ankle muscle peak power, considered as the most reliable 3DGA variable for ankle function. No significant relationships were found between clinical and functional scores on the one hand and ankle power on the other, thereby confirming the absence of a direct link between the structural changes of a joint and its real functional potentiality. The rehabilitation setting, in addition to clinical studies, continues to place much weight on the structural assessment of the joint when considering patient evolution and treatment efficacy. This observation supports the notion that the clinical practitioner should likewise focus on the functional aspects of the joint.

In **Chapter 2**, the natural progression of haemophilic arthopathy was evaluated using 3DGA, with the test-retest reproducibility of this technique being assessed in the patient population. For this, adults with established haemophilic arthropathies were evaluated twice using 3DGA over a time period of 18 weeks. Unexpectedly, the between-period comparison revealed a tendency towards modifying the segmental joint function, but most importantly, an overall infraclinical deterioration of gait pattern, characterized by a minor deterioration of the recovery index, *i.e.*, the pendulum-like mechanism of gait, which is indicative of the subject's ability to save energy while walking. These findings imply that the recovery index may be an integrated indicator for the progression of gait pattern under pathological conditions. This study gives us some indication about the capacity of 3DGA **responsiveness, *i.e.*, sensitivity to change,**when used in cohort studies.

In this study, the **reproducibility** of 3DGA was also assessed by comparing the same rater over time. Testing the reproducibility of 3DGA and estimating the change required to exceed the measurement error are necessary in order to ensure that the error involved in the measurement is small enough to allow for detecting actual changes in the patient's gait. Reproducibility was tested using agreement (Standard Error of Measurement, SEM and Minimal Detectable Change, MDC at 95% confidence interval, MDC_{95}) and reliability (Intraclass Correlation Coefficient, ICC) calculations.ICC provides information about the relative reliability of measurements, but is of limited help when determining if an observed change is due to an actual change in performance [4]. MDC, in contrast, provides a meaningful and practical assessment of measurement errors by providing a single value for each variable in the units of measurements [5].Taking into account the systematic variance caused by the natural evolution of the disease between the two time periods, the main aim of this reproducibility study was not to focus on raw reproducibility scores, but rather to establish a hierarchy of 3DGA variables to be considered with confidence or distrust for future clinical research in the context of this thesis. Gait analysis was sufficiently reproducible regarding spatiotemporal parameters as well as kinetic, mechanical, and energetic gait variables. The kinematic variables were reproducible in both the sagittal and frontal planes.

Gait in patients with haemophilia

Chapter 3 assessed the impact of multiple joint impairments (MJI) of the lower limbs on spatiotemporal, kinematic, kinematic, metabolic, and mechanical variables among a large cohort of PWH. As the ankle is the main joint affected in young PWH despite adequate treatment [6], **Chapter 4** aimed to gain greater insight into the biomechanical consequences of ankle arthropathy. As the aims and methodology of Chapters 3 and 4 are quite similar, the results are discussed together. As walking speed was previously shown to influence gait variables [7], individual patient values were speed normalized in order to identify gait alterations caused by joint impairments, as opposed to changes owing to the different self-selected speeds adopted by our subjects.

An overall elevation of the vertical displacement of the body's centre of mass (CoM) was observed in PWH with MJI and ankle arthropathy. This should have normally resulted in increased mechanical energy being produced in response to the energy changes of the CoM relative to the ground (W_{ext}), as more mechanical energy was needed to redirect the CoM vertically. However, W_{ext} was found to decrease slightly, which may be explained by the strategy of PWH to conserve part of the muscle mechanical work and save mechanical energy via an efficient pendulum exchange between potential and kinetic energy (Fig. 1a), *i.e.*, efficient recovery. In normal walking, recovery attains a maximum of 60-65% at 4-5 km h^{-1}[8], whereas recovery attained up to 70% in subjects with ankle arthropathy walking at lower speeds. Although a recovery index in the normal range was previously reported in patients with isolated orthopedic disorders [9-11], such an improved recovery is quite unusual, being only reported in African women carrying heavy head-supported loads [12]. These experienced head-load carriers were shown to be able to act as a "better pendulum", as they increased their recovery by up to 80% or more. This energy-saving strategy therefore reduced the W_{ext} production, as observed in PWH. In 2002, Cavagna *et al.*[13] showed that, for African women, head-loading significantly improved the transformation of potential into kinetic energy during the descent of the CoM. On the basis of these results, future research should investigate the potential kinetic energy transduction within the step in PWH. In PWH, the pendulum mechanism may therefore be a strategy to help preserve a reasonable amount of the muscle mechanical work and save energy despite significant joint impairments.

Although previous studies paid special attention to the influence of speed-effect on 3DGA parameters, the influence of cadence-related biases on mechanical work production was not taken into account. When a given speed was maintained with longer steps at a lower cadence, W_{ext} increased because the impact against the ground was increased [14]. In contrast, the higher cadence adopted by PWH due to shorter step length could also partially explain the reduction in W_{ext}. When shorter steps and greater cadence were adopted in

patients with the most impaired joints, the limbs were required to accelerate backwards and forwards more times per minute, thus leading to an increase in W_{int}[14]. However, this apparent increase in W_{int} was compensated by the fact that compared to normal, PWH had to perform less mass-specific work to accelerate the body segments, as the reduction in active ROM in arthropatic joints induced a decrease in angular speed and subsequent reduction in W_{int}. Consequently, W_{int} remained in the normal range in MJI or even slightly decreased in PWH with ankle arthropathy. As a result of the unchanged W_{int} and minor reduction in W_{ext}, W_{tot} remained within the normal range in MJI or was reduced in PWH with ankle artropathy.

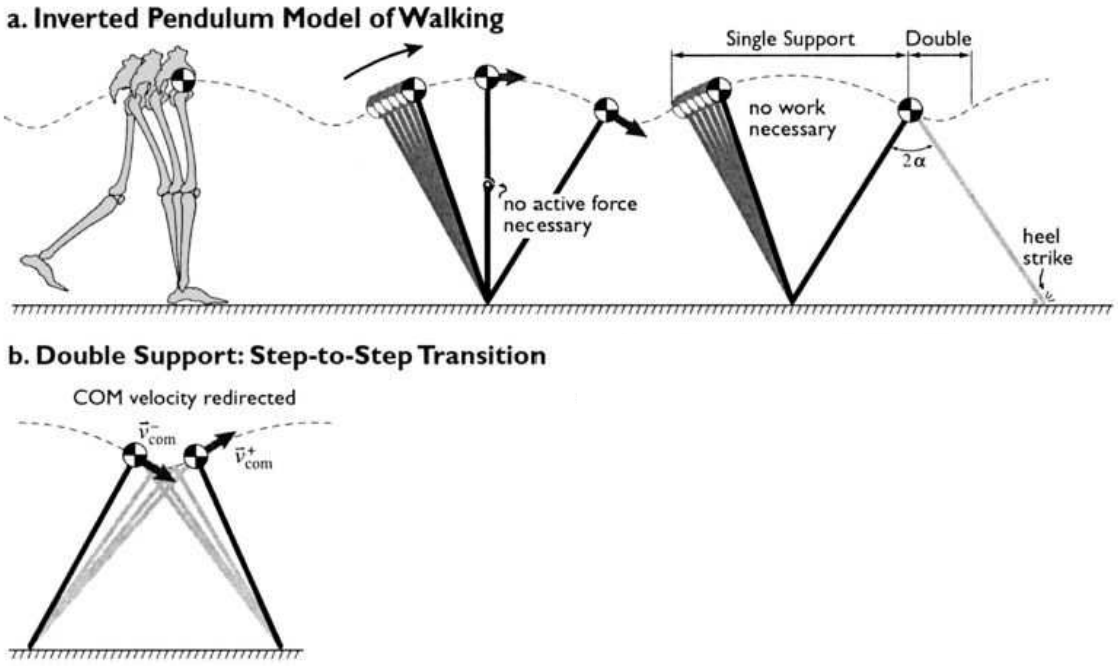

Fig. 1. Schematic diagram of the simple inverted pendulum model of walking, which requires energy to redirect the body's center of mass (CoM) between steps rather than for pendular motion. (a) During single support (when one leg contacts the ground), the pendulum conserves mechanical energy, while the CoM can be supported with no muscle force. Consecutive single-support phases are separated by a double-support phase (commencing with heel strike), as one stance leg is replaced by the other. (b) This is referred to as the step-to-step transition, in which CoM velocity is redirected to a new pendular arc [15].

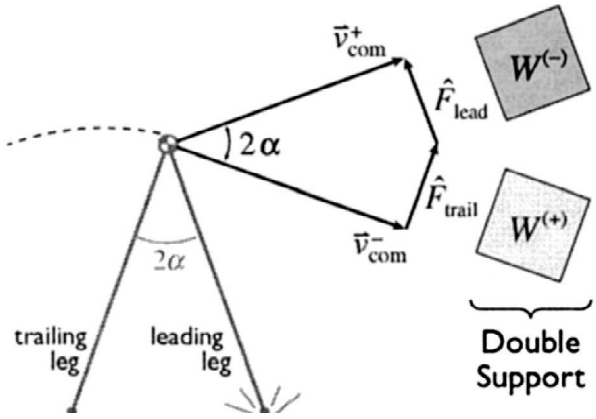

Fig. 2. The CoM velocity redirection by trailing and leading legs During double contact, the back (trail) and front (lead) legs perform positive and negative work on the CoM, respectively. The back and front leg forces (*F* trail and *F* lead, respectively) are assumed to be directed along the legs and are shown separately for the same CoM trajectory [15].

Our results suggested that dramatically PWH increased their mass-specific net cost of transport (C_{net}). In patients with MJI, the increase in C_{net} was proportional to the loss of the active lower limb joint ROM. In patients with ankle artropathy, the increase in C_{net} for PWH was proportional to ankle dysfunction, *i.e.*, the less ankle power was generated during the push-off phase, the more metabolic energy was consumed and more efficiency of walking was impaired. The disruption to the normal walking process by an orthopedic disorder in PWH thus appears to generate mechanical and metabolic changes that follow a continuum.

As W_{tot} remained within the normal range, the elevated C_{net} could not be explained mechanically, contrary to the findings of previous studies on unilateral orthopedic and neurological disorders [9-11;16]. The increase in C_{net} may therefore be due to factors not accounted for in the calculation of W_{tot} in addition to methodological limitations in calculating mechanical muscle work. Usually only the work done to accelerate the body segments relative to the CoM was measured as the standard W_{int}. However, any work that does not impact on the environment nor change the energy level of the CoM is considered W_{int}. There are therefore other sources of W_{int} that were ignored, possibly representing a substantial part of mechanical work. These omissions may therefore have resulted in underestimating the real mechanical work of PWH. Although already discussed in Chapters 3 and 4, these points will be addressed in more detail.

Part of the muscular work may be used to overcome internal friction and viscosity in the ligaments, muscles, or joints in order to deform the body segments. This work is supposed to be greater in PWH as joint stiffness and muscle fibrosis are common complications of arthropathy [17]. This type of W_{int} is, however, not measurable experimentally in *in vivo* conditions.

Some energy may also be associated with the internal step-to-step transition work of the back leg pushing against the front leg during the double contact phase ($W_{int,dc}$) (Fig. 1b and 2)[15;18;19]. In this situation, only the net (sum of positive) work done by the lower limbs during the double contact phase was calculated.Higher muscle forces necessary for $W_{int,dc}$ may require additional metabolic energy (hence, a higher C_{net}) without a parallel increase in W_{ext}[15;20].A better estimation of the real mechanical work of patients may be via the calculation of $W_{int,dc}$, which could be measured with a split-belt treadmill permitting the recording of ground reaction forces of the two legs separately (Fig. 3).

Fig.3. Split-belt treadmill with two force platforms permitting the recording of ground reaction forces of the two legs separately

Another source of W_{int} not taken into account was the work needed to overcome antagonistic co-contractions. However, it may be reasonably hypothesized that these co-contractions are elevated in PWH, as increased activity timing and co-contractions of antagonistic muscle groups were previously identified as a protective strategy in order to maximize joint stability and limit painful ROM in subjects with lower limb impairments [21].Whereas joint moments only allow the net output produced by all muscles spanning a joint to be calculated, they do not permit calculating the force in individual muscles. In this context, surface electromyography (EMG) is one of the few methods that can provide a window on muscle activity and hence muscle force production during functional movements. EMG activation patterns may give an overview of the coordination between multiple muscle groups, while highlighting possible co-contractions. The original design of this work included quantifying the timing and duration of EMG muscular contractions of leg muscles (such as medial and lateral gastrocnemius, tibialis anterior, peroneus longus, and brevis). In the reproducibility study described in Chapter 2, prolonged EMG timing activity of

the leg muscles was visually observed, mainly with regards to the tibialis anterior, thus suggesting the presence of co-contractions. However, the poor reliability of EMG data did not allow us to interpre these results. Future studies should therefore be expanded by investigating the metabolic cost of the co-activation of antagonistic locomotor muscles using a more accurate system.

Is 3DGA a suitable tool to assess the follow-up of articular status in patients with haemophilia?

In light of these methodological and fundamental investigations, 3DGA appears to be a powerful tool to quantitatively characterize the locomotor functions of patients with gait disturbances, including PWH. In **Chapter 5**, 3DGA was used in a clinical trial to objectively quantify the effects of a conservative treatment in PWH with ankle arthropathy.

Foot deformities are common in patients with haemophilic ankle arthropathy and often responsible for discomfort when patients walk or stand for long periods. Currently, there are no validated conservative options for managing haemophilic ankle arthropathy. No study has yet addressed the potential benefits and practicalities of foot orthoses in ankle haemophilic arthropathy. We experimentally investigated the effects of custom-made orthopedic insoles and shoes in PWH with ankle arthropathy, with special attention given to pain and gait.Our study suggested that orthoses may have beneficial effects, as they provide significant pain relief and comfort improvement, with minimal side effects. More specifically, insoles had limited impact on gait pattern, whereas orthopedic shoes significantly improved the propulsive function of the ankle (increased ankle power). Increases in ankle moment and knee flexion in the stance phase also suggested that patients with orthopedic shoes experienced improved weight acceptance, probably due to improved comfort and reduced ankle pain. Biomechanical changes induced by these orthoses were, however, insufficient to influence knee and hip kinematics and kinetics in addition to mechanical and energetic variables.Again, the recovery index was the only mechanical variable that improved slightly when using orthoses.

The ability to distinguish between measurement errors, effects of natural variability in performance over time, and true changes is therefore essential for the successful application of 3DGA for clinical and research purposes. In the light of Chapters 2 and 5, this differentiation was made possible using 3DGA in cohort studies. However, it has not yet been discussed whether 3DGA would be sensitive enough to allow the investigator or clinician to interpret small differences for a same subject when evaluated twice. In this context, the interpretation of MDC allows us to have greater confidence that a real improvement or deterioration exceeds the measurement error, because it is described as the amount of change sufficiently greater than the measurement error for the variable in

question [23]. Variations in gait pattern may occur within the same subject (natural day-to-day gait pattern variation and natural progression of the disease), or in a group of subjects as people simply walk differently. Due to natural fluctuations or disease progression, PWH is expected to demonstrate greater natural variability in performance over time, and as a result, it shows greater MDC values. Whether MDC_{95} values are sufficiently low relates to the 3DGA variable being studied. For example, the MDC_{95} for knee ROM in swing phase calculated in Chapter 2 was 8°,whereas a 6% change was suggested as a meaningful change for the recovery index. Surgical interventions, such as knee replacement, are likely to result in changes greater than MDC_{95} values in knee kinematics, but not for the recovery index, because mechanical variables are probably less sensitive to change compared to spatiotemporal, kinematic, and kinetic variables. The magnitude of the expected intervention effect size context must also be taken into account. More conservative approaches, such as using foot orthoses or anti-inflammatory drugs, may lead to actual, but more subtle gait modifications, resulting in differences inferior to MDC_{95} values.

An implication of our results is that traditional combined limbs measures of W_{ext} and related measures (such as recovery) are poor predictors of metabolic cost because a normal pendular mechanism was observed in all PWH. This is in agreement with the results of Donelan *et al.*[22] who studied the influence of step width on mechanical work and metabolic cost. While the metabolic cost increased until 45% with step width, the W_{ext} did not change significantly because the increases in positive and negative work occurred largely during double support. Combined limb measures such as W_{ext} do not account for such situations. Moreover, the recovery index increased with step width until 76-78%, even though the metabolic costs increased substantially. However, the recovery index seems to be a variable sensitive to change. In the inter-session comparison described in chapter 2, the most relevant change was a 2% decrease in recovery index. Similarly, in chapter 5, the recovery indexwas the only mechanical variable, which improved slightly (between 1 and 3%) when using orthoses.

In summary, 3DGA is a powerful and reliable assessment tool in the context of cohort studies, but probably not in the context of regular individual follow-up, because the subtle changes observed will not exceed MDC_{95} values, especially for mechanical and energetic variables. Regarding this work, two kinds of 3DGA variables may be distinguished: **segmental variables** such as kinematic, kinetic, and spatiotemporal variables, which are probably more sensitive in detecting early changes in limb or joint abnormalities, but provide little information about the gait limitations or disabilities of patients. These issues are better approached using **overall variables**, such as mechanical and energetic measurements, which are considered to be concise and integrated indicators of gait mechanics in addition to being less sensitive to change.

Importance of preserved joint ROM in the economy of mechanical work production and energy expenditure

In addition to the inverted pendulum mechanism, the other strategy aiming to minimize the energetic cost of locomotion is the reduction of the vertical displacement of the CoM. In 1953, Saunders *et al.*[24] postulated that humans minimize the vertical CoM displacement, which minimizes the work required for locomotion and thereby minimizes the metabolic cost. The most economical style of walking would be that the CoM adopts a sinusoidal pathway of low amplitude. Saunders' theory was commonly held in clinical rehabilitation as a general principle until recent experiments [25;26] showed that flat walking costs more energy than normal walking. Therefore, it seems that the more economical mode of walking is an intermediate strategy in CoM displacement between extreme flatness and bouncy walking. The theory proposed by Saunders *et al.*[24] and implemented by Della Croce *et al.*[27] allows us to understand how combined movements of the pelvis and lower limb segments are able to smooth the trajectory of the CoM. Indeed, these specific movements called "gait determinants" produce either limb compression when the CoM reaches its maximum or limb elongation when CoM reaches a minimum position, thus reducing the magnitude of vertical CoM displacement and enabling smooth progression of the body [24;27]. Saunders *et al.*[24] have defined pelvic rotation, pelvic tilt, knee and hip flexion, knee and ankle interaction, and lateral pelvic displacement as the main determinants of gait. Recent quantitative research found new gait determinants: knee flexion of the ipsi- and contra-lateral limbs and heel rise (*i.e.* the third rocker). However, recent experiments found that the third rocker during double stance phase, which was initially thought by Saunders *et al.* to simply smooth out the abrupt inflexion of the CoM trajectory, had the greatest impact and resulted in up to 75% reduction of the vertical CoM excursion, while the other gait determinants accounted for the rest [27]. With the loss of some of the major determinants as a result of multiple joint impairments as seen in haemophilia, the strategy of vertical CoM displacement reduction is compromised leading indirectly to increase in metabolic expenditure. In chapter 3, this theory is confirmed as C_{net} was greater in PWH and directly related to a loss in joint ROM principally at the ankle level.

Methodological considerations

The biomechanical model proposed by Davis was used throughout this thesis to calculate the kinematic parameters [28]. As with all models, limitations exist. Generic kinematic model such as the Davis model used in this work, defines a system of axes associated with each bony segment incorporated in the model, as well as the axes relative motion as a function of the joints degrees of freedom [29]. However, this procedure may introduce errors in calculated kinematics due to 1. Errors associated with palpation of

anatomical landmarks which can affect marker positioning 2. Inaccuracies in the definition of joint coordinate systems (*e.g.* definition of joint centers and axis) [30]. The effect of both error types in kinematic modeling has already been extensively described in the literature [29].

Variability, inaccuracy, and lack of reproducibility due to technical factors must be minimized for 3DGA in order for the technique to be valuable. It is generally accepted that the major source of extrinsic error in 3DGA data is in marker application. Errors may be due to the identification of anatomical landmarks [31]. Correct marker placement is difficult in PWH because some subjects are overweight and/or have joint deformities that lead the palpation difficulties. Overweight patients also have enlarged skin artifacts. However, no marker placement or method for measuring skin-based motion can completely overcome the sources of errors linked to skin motion. We found that total ROM in a specific plane was more reliable than peak values. For example, ankle sagittal ROM at the push-off phase had an ICC of 0.94 and coefficient of variation of SEM (SEM%) of 8%, whereas the values for the maximum ankle flexion at loading response were 0.72 for ICC and 17% for SEM%. These differences may be due to variations in the marker placement, resulting in an offset from flexion to extension, where the total range was in fact unchanged.

Alternatively, more accurate subject-specific kinematic models can now be defined on the basis of MRI [30]. This modeling approach constructs the segmental coordinate systems based on anatomical landmarks identified in the MRI, instead of relying on palpated landmarks and the application of skin markers. Because MRI-based models are based on detailed subject's bony structures, they are significantly less sensitive to both error types. Furthermore, by replacing the reflective markers with markers visible on MRI, the position of markers in segmental reference frames can be accurately defined, therefore allowing corrections for marker misplacement. These MRI-based kinematic models could therefore improve the reliability of 3DGA results, especially in PWH where bony deformations may alter the relative configuration of joint coordinate systems compared to generic models based on normal subjects [30].

It should be also noticed that we analyzed kinetic data only in the sagittal plane. The reasons for neglecting the joint moment (and power) in the frontal and transverse planes were not technical but were rather a precautionary measure for two main reasons. First, the anthropometric data for the determination of moment of inertia and rotation centres of limbs are mainly for the sagittal plane which can induce errors in kinetic calculation for the frontal and transverse planes. Secondly, the lever arm and the forces in the frontal and transversal planes are very small in comparison with those of the sagittal plane. Errors in estimating the lever arm will lead to precision error in the centre of pressure estimation. In general, forces inferior to 10% of body weight such as lateral and frontal forces are not taken into account for the calculation of joint moment. The product of small lever arm and forces can lead us to poor estimation of joint moment.

In chapter 2, the inter-session comparison confirmed a disease progression bias and a systematic error induced by natural progression of the arthropathy during the relative long time interval of 18 weeks. However, it should be reminded that the principal aim of our reproducibility study was not to focus on raw reproducibility scores, but rather to establish a hierarchy of the best reliable 3DGA variables. Moreover, the systematic changes due to disease progression should consequently only induce an underestimation of ICCs. As this inter-session comparison was performed in subjects that already have joint impairments, it should also be mentioned that this reproducibility study may not be generalized for all 3DGA protocols. The reliability results are applicable only for the haemophilia population and only for the Davis model! However, this study supports and extends results of previous work [31;32], emphasizing the high reliability of mechanical and energetic, spatiotemporal parameters, kinetic and kinematic (sagittal and frontal planes) variables.

In this thesis, additional errors occurred when subjects were tested with neutral running shoes and orthopedic shoes. In practice, PWH experience major difficulties when walking barefoot due to foot deformities. In Chapters 3 and 4, the results of PWH walking with neutral running shoes were compared with the normative data for healthy subjects walking barefoot, introducing thus a potential bias. However, a recent systematic review comparing barefoot to shod walking in children reported longer step length and greater ankle and knee active ROM with shod walking, although no significant differences were found in kinetics [33]. In Chapter 5, no difference was found between pre- and post-orthopedic shoe conditions in terms of metabolic cost, mechanical work, and gait efficiency, suggesting that neutral or orthopedic shoes have limited impact on overall gait variables with regard to barefoot conditions.

Our protocol studied gait using an instrumented treadmill. Treadmill gait analysis offers a number of advantages, such as the requirement of less space, precise speed control, and ability to use fewer cameras and acquire consecutive gait cycles for kinematic, kinetic, and metabolic parameters. However, it is debatable as to whether treadmill walking and overground walking are equivalent. The literature suggests that in healthy young and older adults, minor gait differences exist between walking on a treadmill and overground [34;35], although the kinematics and kinetics are reported to be quite similar [36]. Some authors have described increased cadence and decreased stride length [35], while others did not find any differences in terms of spatiotemporal parameters [34]. Nonetheless, in this study, all of the 3DGA trials for PWH and control subjects were performed on a treadmill, thus excluding the bias between treadmill and overground walking.

Walking on a treadmill can also be an unfamiliar experience [37]. This in turn can influence the degree to which measurements obtained from the treadmill are reliable and equivalent to those that would be obtained from overground walking. Reliable 3DGA measurements can be obtained from the treadmill when subjects are given adequate time to familiarize to this initially unfamiliar mode of locomotion. When healthy adults have been

given adequate time to familiarize to the treadmill, reliable kinematic and spatio-temporal measurements can be obtained from treadmill locomotion. In healthy young adults, 4 to 6 minutes of treadmill walking were required to obtain reliable kinematics of the pelvis [37] and knee joint [38] as well as spatio-temporal measurements [38]. In healthy unimpaired older adults, Wass *et al.*[39] found that highly reliable knee joint kinematics and cadence values were achieved by 14 min of treadmill walking. The amount of time required for PWH to familiarize to the treadmill cannot be generalized from findings involving healthy subjects as changes in gait may be affected by multiple joint impairments. In PWH with established arthropathies, a long treadmill familiarization times may be inappropriate due to fatigue and pain. For this reason, a familiarization of at least five minutes was provided to all subjects before the evaluation.

Finally, one major limitation of this study was its sample size, as it was difficult to recruit more patients due to the rarity of haemophilia. Furthermore, the exclusion criteria were very strict (*e.g* .in chapter 5, prior use of foot orthoses). As our sample was small, it should be highlighted that the absence of significance may be due to the low statistical power. In Chapters 3 and 4, individual patient data was compared to the normal values of a control group comprising eight healthy subjects walking at six pre-determined speeds. As observed in Fig. 3 of chapter 3, 3DGA norms often have large standard deviations (SD). This makes normative ranges based on mean ± 2SD rather broad, meaning that many abnormal measurements would be considered normal (false negative). It is reasonable to suppose that increasing the recruitment of healthy control subjects would have probably reduced SD values, leading to an even higher Z-score and more significant differences in Chapters 3 and 4.

Future directions to improve the interpretation of kinematic and kinetic variables

In spite of their objectivity, the interpretation of kinematics and kinetics is complex and time-consuming. Difficulties arise from the complexity of gait and the interdependent nature of gait data. For example, assessing the motions of the lower extremities during a single stride requires the analysis of multiple joints and body segments in multiple planes and at multiple instants of time. To facilitate the use of gait analyses in the clinical setting, the large volumes of data must be reduced and presented in a manner that is both practical and interpretable.

The Gait Deviation Index (GDI) was recently proposed as a valid, robust, and practical measure of overall gait pathology [40-42]. The relevance of the GDI is its ability to capture kinematic deviations in timing, level, and shape for each lower limb independently [42]. Using multivariate measurements, the GDI compares nine kinematic variables of a subject's

gait (pelvis and hip in the three planes, knee and ankle in the sagittal plane, and foot progression, which are identical to the variables calculated in our work) against those of a control group by using the singular value decomposition in 15 “gait features” [41;42]. Calculating the GDI is a simple process, as it can be calculated using the control database of 6,702 strides provided by the authors [42] . A GDI value ≥100 indicates the absence of gait pathology. Every 10 points below 100 corresponds to one SD away from the normal mean. For example, a GDI of 75 represents a gait 2.5 SD below normal.

Although the GDI appears to be a promising tool for facilitating the interpretation of kinematic outcomes, we first decided to verify the possibility of bias related to gait speed and age of the population. Using the excel score sheet provided by the authors [42], we calculated the GDI of 36 healthy subjects constituting the database in our gait laboratory. Healthy subjects walked at six progressive gait speeds and were classified by age group (Table 1).

Normal subjects	1 km h^{-1}		2 km h^{-1}		3 km h^{-1}		4 km h^{-1}		5 km h^{-1}		6 km h^{-1}	
	GDI	Z-score	GDI	Z-score	GDI	Z-score	GDI	Z-score	GDI	Z-score	GDI	Z-score
5 years (N=6)	89.00	-1.10	97.78	-0.22	103.02	0.3	108.48	0.85	not calculated		not calculated	
9 years (N=6)	80.53	-1.95	89.54	-1.05	94.83	-0.52	101.14	0.11	103.68	0.37	100.83	0.08
14 years (N=6)	79.65	-2.03	89.26	-1.07	94.44	-0.56	95.73	-0.43	97.92	-0.21	98.15	-0.18
24 years (N=6)	79.99	-2.00	88.78	-1.12	95.36	-0.46	99.94	-0.01	105.69	0.57	95.65	-0.44
56 years (N=6)	83.55	-1.65	93.52	-0.65	97.78	-0.22	99.09	-0.09	100.46	0.05	92.3	-0.77
77 years (N=6)	76.96	-2.30	83.27	-1.67	87.3	-1.27	93.11	-0.69	86.51	-1.35	not calculated	

Table 1: Mean Gait Deviation Index (GDI) and corresponding Z-score as a function of walking speed in normal subjects. GDI ≥ 100 indicates the absence of gait pathology. Every 10 points that the GDI falls below 100 corresponds one standard deviation away from the normal mean.

These results clearly show the presence of false positives (in orange and red), *i.e.*, healthy subjects classified as having a pathological gait when gait speed falls below 3 km h^{-1}. As our patient group walked at different self-selected speeds, we decided not to use the GDI as a summary index of kinematic variables.

Despite these drawbacks, these techniques for categorizing kinematic patterns are essential and should be implemented in the future, if large volumes of data are to be reduced and presented as both a practical and easy-to-interpret assessment tool in intervention studies with large cohorts of subjects.

A few months ago, the GDI-Kinetic was developed similarly to the method used to derive kinematics [43]. The GDI-Kinetic is a direct analog of the GDI based on joint kinetics rather than kinematics. The method consists of identifying ‘‘features’’ of the raw gait kinetic data using singular value decomposition, identifying a subset of features that account for a large percentage of the information in the raw gait kinetic data, expressing a subject’s raw

data as a linear combination of these features, and calculating the magnitude of the difference between the subject and the mean of 8488 strides of a healthy control group. Although the GDI and GDI-Kinetic provide a global measure of gait pathology, some differences are present between them. The relatively low correlation coefficient between the GDI and the GDI-Kinetic indicates that for any given level of GDI-Kinetic, there can be a wide variety of kinematic patterns and vice versa; suggesting each index is measuring a different aspect of gait pathology [43]. The GDI-Kinetic thus complements the GDI, giving a more comprehensive measure of gait pathology.

Directions for future research

Most probably due to recruitment difficulties, relatively few studies have focused on gait disorders in patients with haemophilia. Recently, Stephensen *et al.* [44] published the first 3DGA study integrating both kinematic and kinetic variables in children with haemophilia. Although focused on the sagittal plane alone, the authors reported significant changes in kinematics and kinetics in children with haemophilia compared with age-matched healthy controls. Their results suggested that early biomechanical changes were present in children with a history of target joint bleeding, while lower limb joint function was more impaired than the current clinical evaluation suggested, confirming the previous observations reported by Bladen *et al.*[45]. Using a simplified gait analysis system, the authors reported abnormalities in spatiotemporal parameters in asymptomatic children with haemophilia, and additional significant differences in children with established arthropathy.

With respect to the **pediatric** population, preliminary data from our group reported that in clinically asymptomatic children with a previous history of joint bleeds, kinematic and kinetic response to perturbations may be observed, principally at the ankle level.Over the past decade, it has become apparent that the reduction of the foot to a single segment, as in the Davis model, oversimplifies its role in lower limb dynamics during gait. The motion of the foot and ankle joints are complex and difficult to quantify unless using more sophisticated multi-segment foot models [46]. Indeed, these models have revealed that skin-mounted markers may consistently, and with a good degree of repeatability, detect significant amounts of motion at the major joints in all three anatomical planes. To further complement this research, further investigations are required in order to test the sensitivity of these models for detecting the onset of arthropathy in **young PWH** and compare this functional assessment with a thorough radiological evaluation using magnetic resonance imaging and ultrasonography.

Appendixes:

Details of Methods

1. Ground reaction force decomposition

In clinical research and routine gait analysis, ground reaction forces (GRF) are commonly recorded by means of floor-mounted force platforms in order to compute net joint moments and powers. In our protocol, a force measuring treadmill, *i.e.*, a forceplate mounted underneath the treadmill belt, recorded the summed GRF from both feet. During walking, approximately 20-25% of the time is spent in double foot contact (introduction, fig. 11). During these double stance phases, the measured GRF is a summation of GRF under the left and right feet. In order to estimate the vertical forces under each foot, a decomposition of superimposed horizontal and vertical GRF into left and right force profiles was computed by using an algorithm based on the idea of Davis and Cavanagh [47]. So the left and right GRF profiles and centres of pressure (CoP) must be computed from the global values of the GRF and CoP. The method decomposes the left and right GRF and CoP profiles from the global values of the GRF and corresponding CoP. This method is based on the examination of the side-to-side oscillations of the global CoP corresponding to the measured global GRF.

Raison *et al.*[48] compared the position of the CoP of six subjects walking overground on seven independent platforms to that obtained from a single “virtual” platform corresponding to the sum of the GRF recorded by these seven platforms. CoP trajectories were similar with both methodologies. Vertical and horizontal force signals when walking overground on a single “virtual” platform were also compared to those obtained on the seven independent platforms [48]. The mean error in vertical force signals was 4% during the double support phase, with a maximal error of 9% during this phase. The horizontal force was underestimated on the single “virtual” platform during the double support phase, and the maximal error was around 60%. The underestimation of the horizontal force during the double support phase had only small effect on joint moment. Indeed, horizontal force is a small component of the total GRF (around ten times smaller than the vertical force). Moreover, this error is limited to the double support phases. To assess the impact of this error on moments, Stoquart *et al.*[49] tested the ankle moment in three subjects walking at 1 and 5 km h^{-1} and computed by three different ways. The first one computed the algorithm used in the present thesis, the second one doubled horizontal force during the double support phase to approximate a correction of the underestimation, and the third one neglected horizontal force during the double support phase. Ankle moments were similar in all conditions, demonstrating that horizontal force only represent a small part of the ankle joint moment computation. During the double support phase, the ankle moment computed following the third method was 3% (1 km h^{-1}) and 6% (5 km h^{-1}) lower than following the two other methods.

2. Measurements of the energy consumption during walking

The overall energy consumption of the body is classically measured by the indirect calorimetry method. This method estimates the energy consumed by metabolic processes from the exchange between oxygen (O_2) consumption and carbon dioxide (CO_2) production in open-circuit spirometry with an ergospirometer (Quark b^2, Cosmed, Italy). Values are automatically converted to standard temperature, pressure and dry oxygen consumption. After steady state was reached, metabolic data are collected. The volume of O_2 and CO_2 breathed during a specific period of time are used to compute the Respiratory Exchange Ratio (RER), *i.e.*, the ratio between the rate of CO_2 production and the rate of O_2 consumption [50]. The RER varies as a function of the metabolized substrates, and it can be used to estimate the energetic equivalent of O_2, *i.e.*, the energy produced when one liter of O_2 is consumed, depending on the oxidized substrate. With this method, the measured O_2 consumption (l kg^{-1} min^{-1}) is converted into energy consumption (J kg^{-1} min^{-1}) and the total mass-specific gross energy consumption rate (W kg^{-1}) is determined using Lusk's equation [51]:

$$\mathbf{kJ/lO_2 = (16.1 + 5*RER)}$$

Only trials with RER≤1.0 were retained and analyzed. Energy consumption is usually expressed in terms of power or in term of cost. The metabolic power in the energy consumed per unit of time and body weight (W kg^{-1}). The mass-specific net energy consumption rate (W kg^{-1}) was calculated from the energy consumption attributed to the walking, *i.e.*, the energy consumption rate while walking minus the energy consumption rate while standing. The mass-specific net cost of transport (C_{net}) corresponds to the power divided by the walking speed (in m s^{-1}) and, consequently, to the energy consumed per unit of distance (J kg^{-1} m^{-1}).

Metabolic data were continuously measured during the experiments. A baseline standing metabolic rate was taken at the beginning of each measurement session, for at least 3 min. Each walking trial was maintained as long as necessary to obtain a steady metabolic state for at least 3 min, during which we simultaneously collected metabolic, kinematic, kinetic data and mechanical work of 10 consecutive walking strides.

3. Calculation of the internal mechanical work

The internal work (W_{int}), the work performed to move the limbs relative to the CoM during gait, was computed from kinematic and anthropometrical data following the method described by Willems *et al.*[52]. The displacement of passive reflective markers placed on the acromion (AC), the greater trochanter (GT), the lateral condyle of the knee (LCK), the head of the fibula (HF), the lateral malleolus (LM), and the base of the fifth metatarsal (FM), was filmed using the optoelectronic system (Elite-V5 system, BTS, Italy) with six cameras at a sampling rate of 100 Hz. The body was divided into seven rigid segments: head-arm-trunk (HAT) (AC-GT), thighs (GT-LCK), shanks (HF-LM) and feet (LM-FM). Anthropometrical tables of Winter [53] were used to determine the position of the center of mass of each body segment. The internal mechanical energy of the body segments corresponded to the sum of the rotational and translation energies of these segments due to their movements relative to the CoM. For each lower limb, the internal mechanical energy curves of the thigh, shank and foot were summed ($Ei_{,RLL}$ and Ei_{LLL} on Fig. 1). The W_{int} of each lower limb and HAT segment were then calculated separately as the sum of the increments of the respective internal mechanical energy curves during one stride. Finally, the W_{int} during gait corresponded to the sum of the W_{int} done to move the lower limbs and the HAT segment and was expressed per kilogram body mass and per metre travelled (Fig 1).

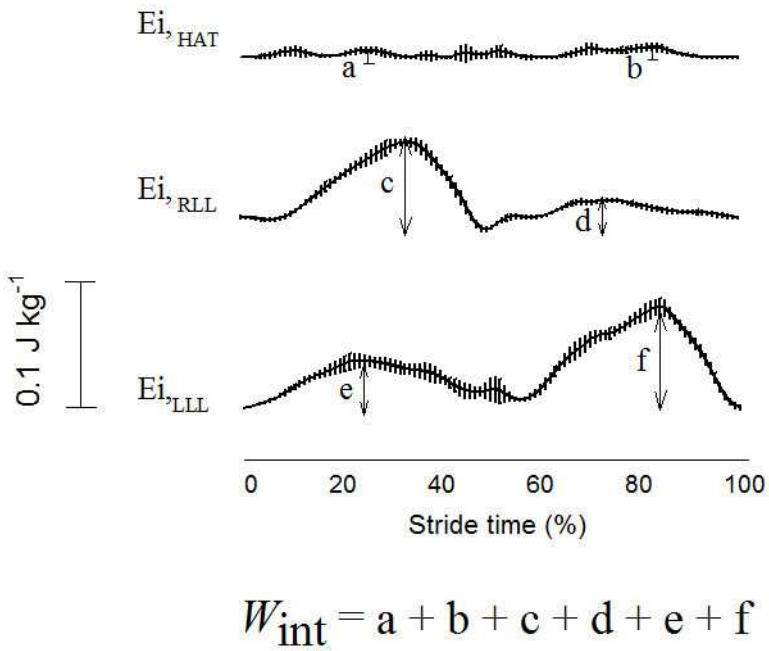

Fig. 1. Curves of internal energy as a function of time. These curves were used to compute the W_{int} required to move the limbs relative to the CoM for the Head-Arm-Trunk (HAT) segment ($Ei_{,HAT}$) as well as the left and right lower limb segments ($Ei_{,RLL}$ and $Ei_{,LLL}$). For each lower limb, the internal mechanical energy curves of the thigh, shank and foot were summed. When the curves increase, the muscle provides positive work to accelerate the body segments relative to the CoM. The W_{int} during gait corresponds to the sum of the W_{int} done to move the lower limbs and the HAT segments, and it is expressed in joules per kilogram body weight and per meter travelled. The a, b, c, d, e, and f vertical arrows show the increments of the internal mechanical energy curves.

In our study, the W_{int} attributed to the arms was neglected. However it only represents a slight underestimation of the real W_{int} performed. For instance, from the data of the article of Willems *et al.* (Fig. 2), we estimated that the part of W_{int} attributed to arms is 14.5% at 4.5 km h^{-1}.

The decomposition of W_{int} at 4.5 km h^{-1} is as follow:

$W_{int,foot}$ = 7.1J * 2 = 14.2J

$W_{int,leg}$ = 8.5J * 2 = 17J

$W_{int,thigh}$ = 5.7J * 2 = 11.4J

$W_{int,lower\ arm}$ = 2.8J * 2 = 5.6J

$W_{int,upper\ arm}$ = 0.8J * 2 = 1.6J

Furthermore, this under-estimation of the real W_{int} performed is attenuated at lower speed as cadence and amplitude of upper limbs' movements are reduced.

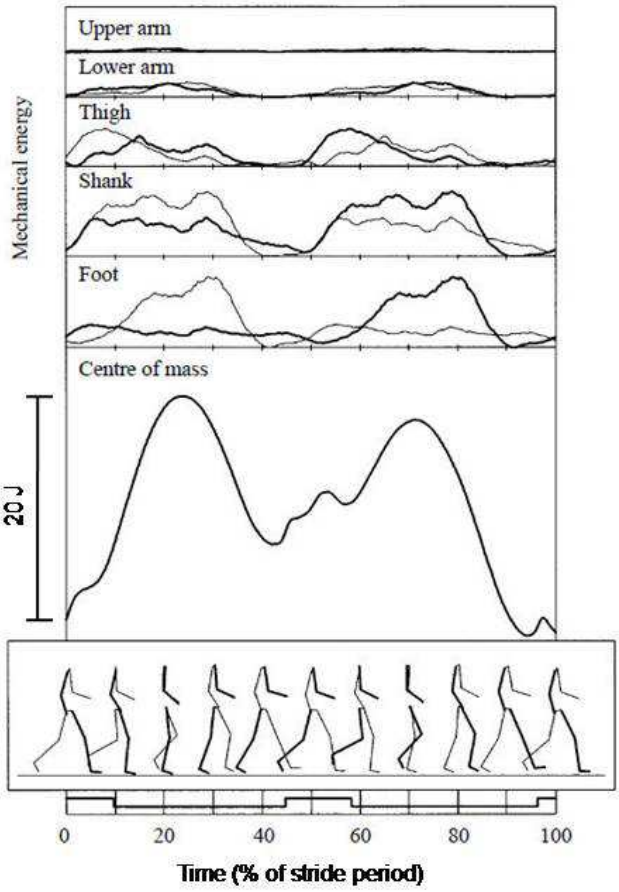

Fig 2. E_{kf} changes of the limb segments due to their velocity relative to the CoM for one subject at 5.4 km h^{-1}. Adapted figure from Willems *et al.*[52]. Thick lines indicate the position and E_{kf} of the segments closest to the camera. The E_{kf} of the arms is represented by the summation of the top two traces.

4. Calculation of the external mechanical work

The external work (W_{ext}), the work performed to lift and accelerate the CoM relative to the surroundings during gait, was computed from the measurement of the GRF following the method described in detail by Cavagna [54] and Willems *et al.*[52]. The vertical, forward and lateral GRF were recorded by means of the strain gauges of the force measuring treadmill at a sampling rate of 100 Hz and were digitized synchronously with the Elite system. The 3D accelerations of the CoM were computed from the vertical, lateral and forward components of the ground reaction forces and the mass of the subject. The mathematical integration of the 3D accelerations gave the velocity changes of the CoM in all three directions (V_v, V_f, V_l). From the instantaneous V_v, V_f, V_l and the body mass (M), the instantaneous vertical ($E_{kv}= 1/2MV_v^2$), forward ($E_{kf}= 1/2MV_f^2$) and lateral ($E_{kl}= 1/2MV_l^2$) kinetic energies of the CoM were computed. A second mathematical integration of V_v was performed to determine the vertical CoM displacement (S_v) of the CoM. The amplitude of vertical CoM displacement was measured as the peak-to-peak amplitude on the S_v curve over a stride. A stride was selected for analysis only when the sum of the increments in V_v, V_f, V_l changes did not differ by more than 25% from the sum of the decrements, thus indicating a relatively constant average height and speed per stride [54]. The instantaneous gravitational potential energy ($E_p= MgS_v$) was computed from the S_v of the CoM, the body mass and the gravity constant (g). The total external mechanical energy (E_{ext}) of the CoM was calculated as the sum of E_{kf}, E_{kv}, E_{kl} and E_p. The increments of the E_{kf}, E_{kv}, E_{kl} and E_p curves respectively represented the positive work (W_{ekf}, W_{ekv}, W_{ekl} and W_{ep}) necessary to accelerate the CoM in the three directions and to lift the CoM during a stride. W_{ext} was obtained by summing the increments of E_{ext} over a stride (Fig. 3). W_{ekf}, W_{ekv}, W_{ekl}, W_{ep} and W_{ext} were expressed per kilogram body mass and per distance travelled.

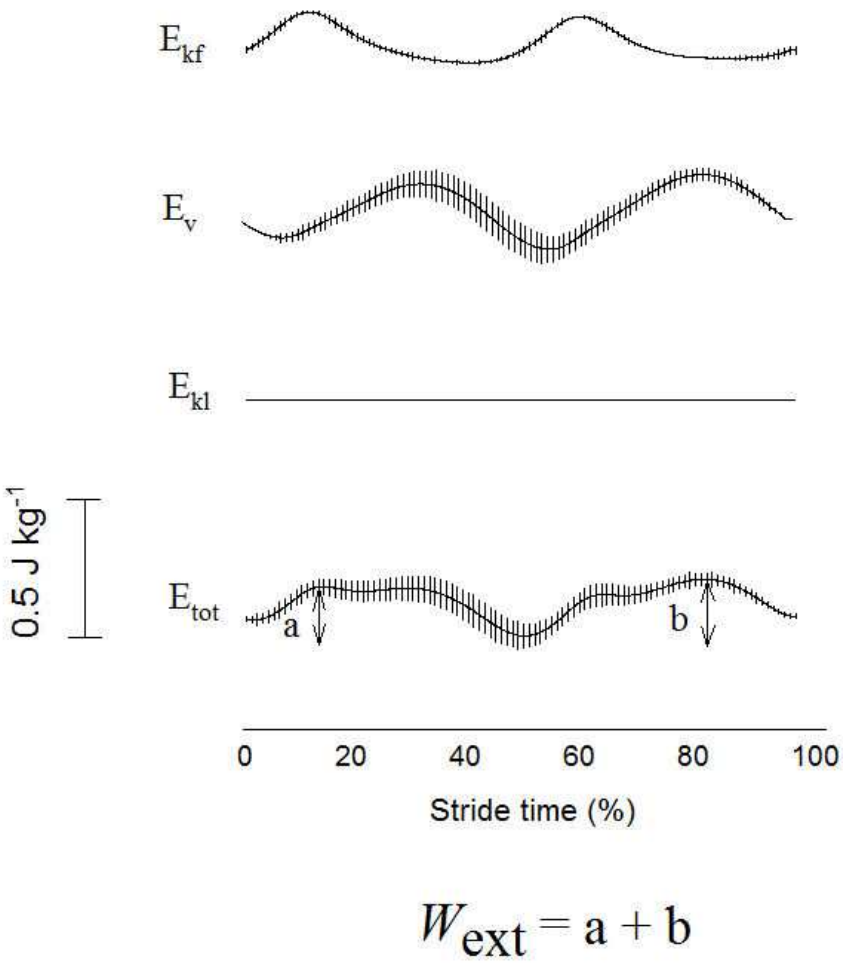

Fig 3. Curves of external energy as a function of time. These curves are used to compute the external work (W_{ext}) performed by the muscles to accelerate and lift the CoM relative to the surroundings. The E_{kf} curve represents the kinetic energy variations related to the speed of CoM displacement in the forward direction. The E_v curve represents the gravitational potential (E_p) and kinetic energy variations (E_{kv}) related to the speed of CoM displacement in the vertical direction. The E_{kl} curve represents the kinetic energy variations related to the speed of CoM displacement in the lateral direction. The total mechanical energy (E_{tot}) of the CoM is calculated as the sum of the kinetic and potential energies. The increments of E_{kf}, E_v and E_{kl} curves represents the positive work (W_{ekf}, W_{ev} and W_{ekl} respectively) necessary to accelerate the CoM in the three directions and lift the CoM during a stride. W_{ext} is obtained by summing the increments of E_{tot} over a stride. The a and b vertical arrows show the increments of the external mechanical energy curves.

5. Calculation of the recovery index

In walking, the CoM is lifted up and down during the stride. It reaches its highest position during mid stance and its lowest position during the double stance phase. The CoM also accelerates and decelerates successively during the stride and reaches its minimum forward speed during mid stance and its maximum forward speed during the double stance phase. Both the energy used to accelerate (E_{kf}) and to lift up the CoM ($E_v = E_p+E_{kv}$) oscillate between a maximum and a minimum value. They are more or less out of phase (Appendix 4, fig. 3), allowing transformations between E_{kf} and E_v, like in a pendulum. This mechanism allows the recovery of a fraction of the mechanical work done by muscles. This explains why

the fluctuations of E_{tot} are smaller than the sum of the fluctuations of E_v and E_{kf} and, consequently, why the W_{ext} is smaller than the sum of the W_{ev} and W_{ekf}.

The 'recovery' quantifying the percentage of mechanical energy saved via a pendulum-like exchange between gravitational potential energy and kinetic energy of the CoM was calculated as detailed in Willems *et al.* 1995 [52]:

$$Recovery(\%) = 100 \times \frac{W_{ekf} + W_{ekv} + W_{ekl} + W_{ep} - W_{ext}}{W_{ekf} + W_{ekv} + W_{ekl} + W_{ep}}$$

A 100% recovery would require the kinetic and potential curves to be exactly out of phase and of equal shape and amplitude according to an ideal frictionless pendulum.

6. Estimation of joint moments by inverse dynamics

The net muscular moment is the resultant of all moments generated by agonist and antagonist muscles, passive structures of the joint and frictional articular forces. The moments can be derived from the kinematics using the Newton and Euler equations [55]:

Newton (linear): F = m.a (Force = mass x linear acceleration)

Euler (angular): M = I.α (Moment = mass moment of inertia x angular acceleration)

These equations describe the so-called inverse dynamics because we use the kinematics to derive the kinetics responsible for the motion. Inverse dynamics is based on several assumptions:

- that the joints are frictionless joints
- that the segments are rigid with mass concentrated at their centres of mass
- that there is no co-contraction of agonist and antagonist muscles
- that air friction is minimal

Several body segment parameters are required to be known, such as the relative masses and mass moment of inertia of each segment and the positions of their centres of mass. These are mainly determined from published cadaver studies, though it is nowadays possible to estimate the body segment parameters of an individual more directly from MRI [30;56;57]. Our laboratory still relies on the cadaver regressions of Dempster *et al.*[58].

Joint reaction forces estimation (Fig. 4)

From Newton, Sum of horizontal Forces, $\Sigma F_x = m.a_x$:

$R_{xp} = m.a_x - R_{xd}$

Where p = proximal, d = distal joint, a_x = acceleration of segment CoM in forward direction

From Newton, Sum of vertical Forces, $\Sigma F_y = m.a_y$:

$R_{yp} = m.a_y + mg - R_{yd}$

Where p = proximal, d = distal joint, a_y = acceleration of segment CoM in vertical direction

Joint moment estimation (Fig. 4)

From Euler, Sum of Moments, $\Sigma M_z = I\alpha$ (where α = angular acceleration)

$M_{zp} = I_z.\alpha - M_{zd} - Rxp.(y_p-y_{CoM}) + R_{yp}.(x_{CoM}-x_p) + R_{xd}.(y_{CoM}-y_d) - R_{yd}.(x_d-x_{CoM})$

Where (x_{CoM}, y_{CoM}) are the co-ordinates of the centre of mass of the segment, (x_p, y_p) the coordinates of the proximal joint (x_d, y_d) the coordinates of the distal joint

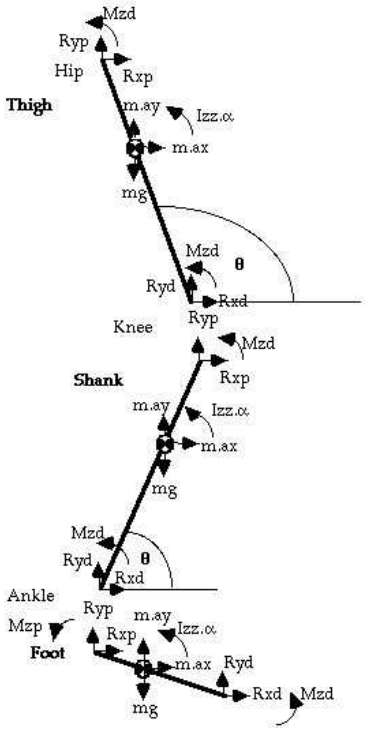

Fig. 4. Diagram used to calculate the net moment of a joint.

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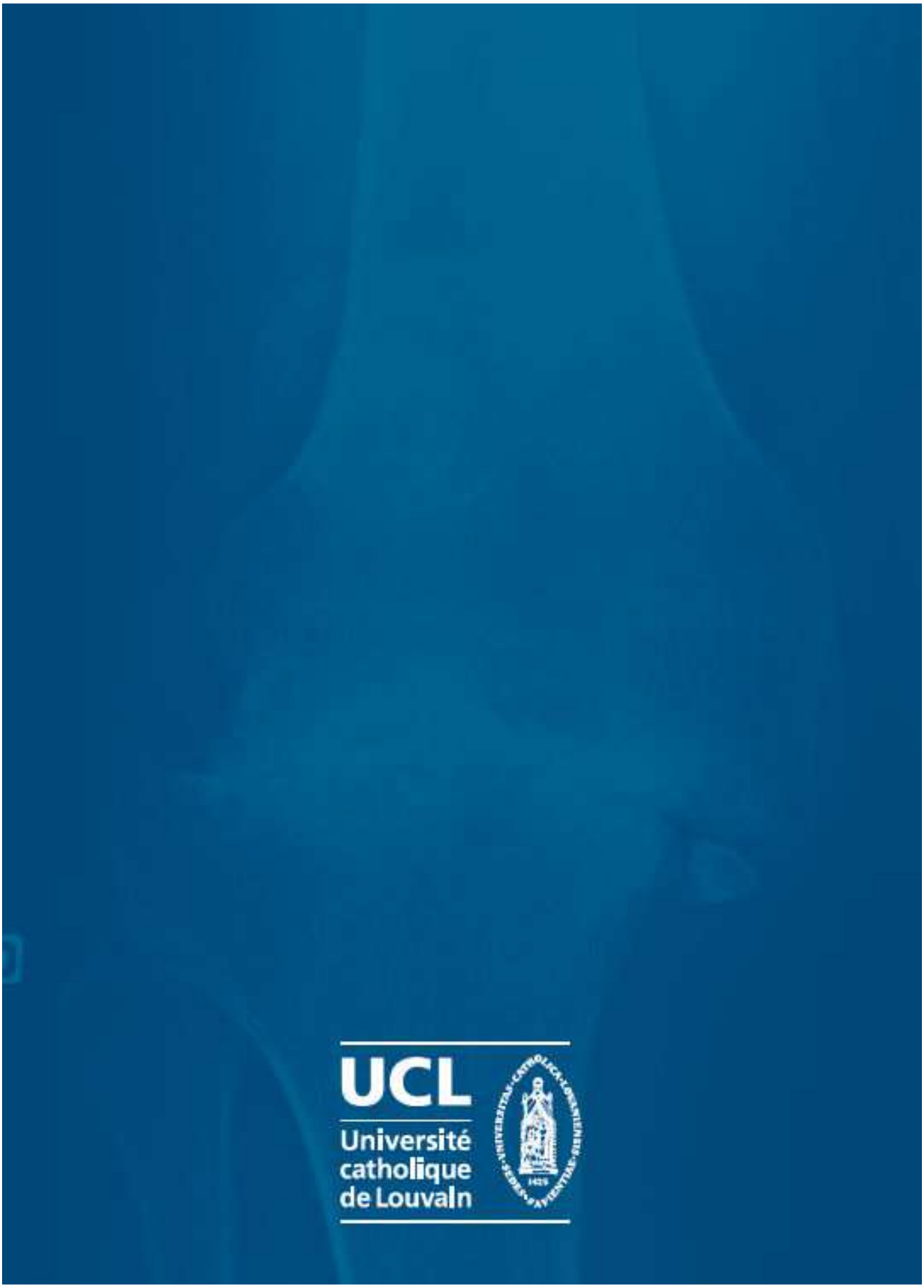
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